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Mechanistic Rationale for the $NaBH_4$ Reduction of α-Keto Esters

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Abstract : An intramolecular hydride delivery process largely contributes during the double reduction of α-keto esters into diols by $NaBH_4$. In the case of enolic α-keto esters, the first step of the process, the reduction of the keto group, occured exclusively through an 1,2-hydride addition despite the predominance of the tautomeric enolic form. The clear-cut difference of reaction rate between enolic and non enolic substrate 4 for reaction carried out in methanol is interpreted in terms of competitive hydride consumption due to the extremely favorable reaction between this solvent and $NaBH_4$.

Sodium borohydride is an inexpensive reagent for the mild reduction of carbonyl as well as imino compounds, and it is thus widely used in organic synthesis.[1,2] Esters generally do no react with this reagent[3]. However, it has been shown that reduction of α-hydroxy esters[4], α-[5,6] and β-keto esters[7] to 1,2- and 1,3-diols, respectively, as well as that of α-amino- esters[8] and acids[9] to amino alcohols does occur using $NaBH_4$. A possible mechanism for the $NaBH_4$ reduction of the ester function of these α- or β-functionalized esters[4-9] may involve an intramolecular hydride delivery[10,11]. In the development of these reactions, the authors were mainly interested in the synthetic aspect, and no hence unambiguous evidence for an intramolecular process was advanced[10]. We have recently reported a remarkable solvent effect which enabled us to control the mono- or the double reduction of enolizable α-keto esters with $NaBH_4$, providing either α-hydroxy esters **2** or diols **3** with a high level of selectivity[5]. Reactions conducted with one equivalent of sodium borohydride in methanol stopped at the mono reduction stage, producing α-hydroxy esters **2** almost exclusively. However, in ethanol, diols **3** were exclusively obtained. In the latter case, an excess of reducing agent (3 equivalents) was required to drive the double reduction to completion within a reasonable time period. For these reactions, we postulated, for the first time, an intramolecular hydride delivery as a possible pathway. Indeed, we initially postulated a mechanism involving the formation of an alkoxyborohydride species (**A** in Scheme 1, eq 1) resulting from the reduction of the keto group, which depending upon the reaction conditions may be further involved in reduction of the ester function (Scheme 1). Further experiments were necessary to confirm this mechanistic speculation, since several obscure points, summarized in Scheme 1, eqs 1 and 2, remained to be solved. Our study focusing on these points is reported herein. Thus, we provide evidence that the $NaBH_4$ reduction of α-keto esters proceeds first *via* a 1,2-hydride addition of the keto group, followed by an intra- (or intermolecular) hydride addition to the ester moiety.

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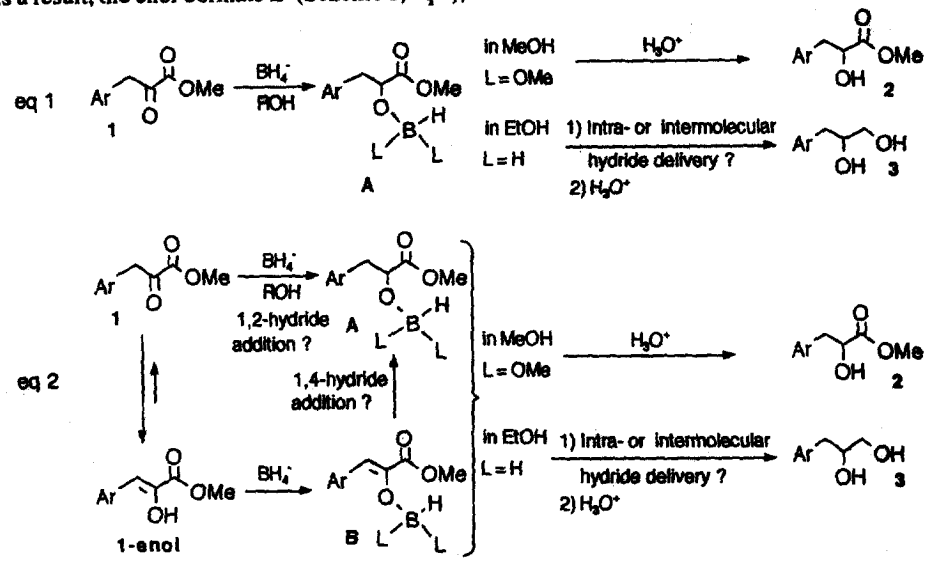
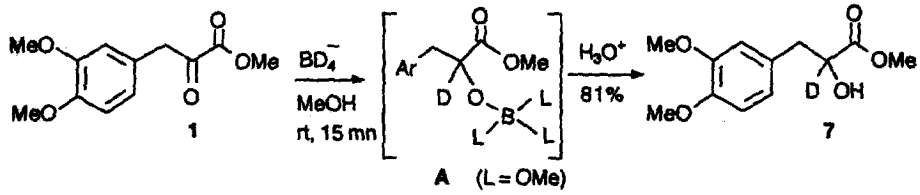
Beside the question of intramolecularity, one of the main problems lies on the fact that ^{1}H and ^{13}C NMR spectra of type **1** compounds revealed only the enol form, regardless of the solvent used ($CDCl_3$ and MeOD-d^4). As a result, the enol borinate **B** (Scheme 1, eq 2), could well be an intermediate in the reaction[12].



Scheme 1

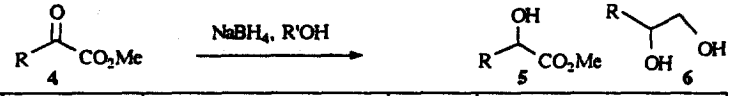
To resolve this question, the methyl 2-oxo 3-(3,4-dimethoxyphenyl) propanoate **1**, previously used as a model[5], was treated with one equivalent of deuteriated sodium borohydride in methanol. This reaction led to the formation of one product **7** corresponding to **2**, in which deuterium has been incorporated at the α position relative to the ester function, as shown by ^{1}H NMR spectroscopy after comparison with the ^{1}H spectrum of **2** itself. Both the absence of the signal at 4.42 ppm corresponding to the hydrogen adjacent to the hydroxyl and the ester groups and the disappearance of the ^{3}J coupling constants between this hydrogen and the two distincts benzylic protons unambiguously showed that deuterium has been incorporated at the homobenzylic position. This result supports the 1,2-hydride addition pathway *vs* the 1,4 one as the first step in the reduction of α-keto esters (Scheme 1, eq 2). This was confirmed by other further experiments involving the $NaBH_4$ reduction of the methyl and the methoxymethyl (MOM) enol ethers of **1**. Upon treatment with 3 equivalents of the reducing agent in ethanol for 24 hours, these latter left untouched at their olefinic bond, and the corresponding allylic alcohols were obtained in only 30% yield.



Scheme 2

We next focused on evaluating the viability of the intramolecular hydride delivery pathway. Therefore, we investigated the borohydride reduction of non-enolizable α-keto esters. One pyruvate derivative, the methyl

benzoyl formate **4**, was chosen as a typical non-enolizable α-keto ester for this purpose. The results obtained through reduction of **4** in various conditions are collected in Table 1.



entry	substrate	conditions	reaction time	α-hydroxyester yield[b]	diol
1[ref. 4]	R = $ArCH_2$ **1**	1 eq. $NaBH_4$, MeOH, rt	1h	91% **2**	-
2[ref. 4]	R = $ArCH_2$ **1**	3 eq. $NaBH_4$, EtOH, rt	"	-	**3** 96%
3	R = Ph **4**	1 eq. $NaBH_4$, MeOH, rt	30 min	-	**6** 94%
4	R = Ph **4**	0.6 eq. $NaBH_4$, MeOH, rt	"	72% **5**	**6** 28%
5[a]	R = Ph **4**	1 eq. $NaBH_4$, MeOH, rt	"	85% **5**	-
6	R = Ph **4**	1 eq. $NaBH_4$, MeOH, -30°C	1h	88% **5**	-

a : $NaBH_4$ and MeOH were previously allowed to stirr together 15 minutes before adding the keto ester. b : Yields of pure isolated products except for entry 4 where the ratio **5** / **6** was determined by ^1H NMR on the basis of the relative integrations.

Table 1

In sharp contrast to the enolizable ketone **1**[5] (reported for comparison in Table 1, entries 1-2), the reduction of **4** specifically provided the corresponding diol **6** under the conditions previously defined to obtain the hydroxy esters (1 equivalent of reducing agent in methanol, entry 3). However, when less than 1 equivalent of sodium borohydride was used, **4** was converted to α-hydroxy ester **5** as the major product (72%) along with a non-negligible amount of **6** (28%) (entry 4).

As for the enolizable ketone **1**, the course of the reduction could be controlled. Indeed, allowing $NaBH_4$ to react with methanol for 15 minutes before adding a solution of **4** in methanol afforded the α-hydroxy ester **5** exclusively (entry 5), suggesting that most of the hydride was consumed by reaction with methanol. The high yield of mono-reduction product (88%) obtained, and the fact that no diol was detected indicated that at least 3 of the 4 hydride atoms bound to boron were displaced by a methoxy group (Scheme 1, intermediate **A** with L = OMe). The known reaction of $NaBH_4$ with methanol is thus an important process competing with the reduction of the α-keto ester. Thus, without any aging, lowering the reaction temperature might modify the relative rates between the reaction of $NaBH_4$ with methanol and the different steps involved in the double reduction process. In this situation, the course of the reduction may deviate from the classical mechanism. Indeed, when the reduction was performed at -30°C, the α-hydroxy ester **5** was again obtained in good yield (entry 6). Although a period of one hour was required in these conditions for the total disappearance of the starting material, only a trace of diol was detected by thin layer chromatography (tlc). This result indicated that hydrogen formation, resulting from the reaction between methanol and any borohydride species is faster at this temperature than ester reduction.

The surprising and facile formation of diol **6** observed in these experiments suggests an intramolecular process for the $NaBH_4$-mediated transformation of α-keto esters to diols, since **6** can be obtained specifically in the presence of only 1 equivalent of $NaBH_4$. In such an intramolecular process, the hydride and the ester functions might be brought together in close proximity, allowing a facile intramolecular hydride transfer *via* a cyclic five-membered transition state. AM_1 Calculations[13] strongly support such a cyclic

transition state as the probable intermediate. Indeed, the short distance found between one of the hydrides and the ester carbonyl (0.262 nm) suggests the feasability of the intramolecular hydride delivery. Moreover, in this transition state, the incoming hydride is ideally placed relative to the carbonyl group so as to follow the Bürgi-Dunitz trajectory appropriate for such nucleophilic additions (Figure 1)[14].

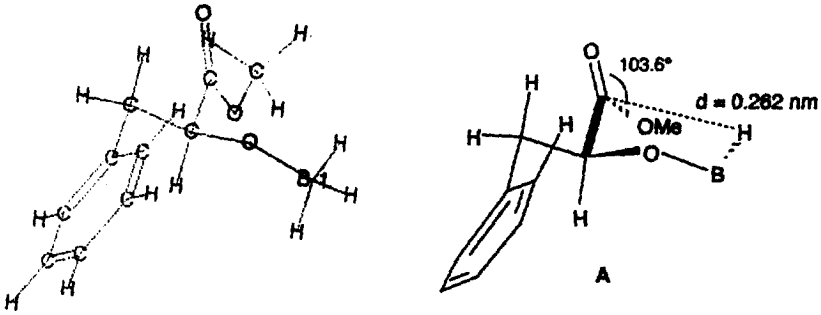


Figure 1 : Calculated cyclic five membered ring alkoxyborohydride transition state A

In conclusion, we have demonstrated the viability of the intramolecular process in the reduction of α-keto esters to diols by $NaBH_4$. From our results, we can unambiguously conclude that the first step of this general process is a 1,2-hydride addition to the keto group. With non enolizable α-keto ester **4**, this 1,2-hydride addition is extremely rapid and the favorable intramolecular hydride delivery to the ester carbonyl occurs in methanol. With enolic substrates, the keto reduction proceeds more smoothly and allows a competitive consumption of sodium borohydride by the alcoholic solvent. In methanol, which is particularly reactive towards $NaBH_4$, this leads to the formation of alkoxyborate intermediates, hydrolysis of which gives solely an α-hydroxy ester. With the less reactive ethanol as the solvent, diols were obtained specifically. By close analogy, the facile reduction of α- and β-functionalized esters[4-8] and acids[9] may be rationalized by a similar intramolecular hydride delivery pathway.

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