Lanthanoids in Organic Synthesis. 6. The Reduction of α-Enones by Sodium Borohydride in the Presence of Lanthanoid Chlorides: Synthetic and Mechanistic Aspects

André L. Gemal and Jean-Louis Luche*

Contribution from the Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité (LEDSS), Bâtiment de Chimie Recherche, Université Scientifique et Medicale, BP 53 X, 38041 Grenoble Cédex, France. *Received February 17, 1981*

Abstract: Lanthanoid chlorides ($LnCl_3$) are efficient catalysts for the regioselective 1,2 reduction of α-enones by $NaBH_4$ in methanol solution. Optimal conditions of this reaction have been determined. A mechanistic interpretation depicting the role of the Ln^{3+} ions is given. The major effect of Ln^{3+} is the catalysis of BH_4^- decomposition by the hydroxylic solvent to afford alkoxyborohydrides, which may be responsible for the observed regioselectivity. The stereoselectivity of the process is also modified by the presence of the Ln^{3+} ions, in that axial attack of cyclohexanone systems is enhanced.

Since the discovery of the reducing properties of boron hydrides, sodium borohydride has received considerable attention as a selective and mild reducing agent of the carbonyl group. A large variety of papers report results of synthetic, mechanistic, or stereochemical importance, and reviews have recently been published.[2]

The question of the mechanism, especially in an alcoholic solvent, is intriguing and complex since as the reaction proceeds various alkoxyborohydrides **1** are produced, which may react with their own stereo- and regioselectivities. Disproportionation of some or all alkoxyborohydrides to BH_4^- further complicates the situation. The problem has been extensively studied theoretically[3] as well as by stereochemical and kinetic approaches.[3,4] Other studies demonstrate that the usual reaction selectivity of $NaBH_4$ can be substantially modified by addition of various metal salts, such as aluminum,[5] cobalt,[6] copper,[7] nickel,[8] tin,[9] titanium,[10] and zinc,[11] to give complex reagents, which are capable of synthetically useful conversions including the reductions of acyl chlorides to aldehydes,[7] olefins to saturated hydrocarbon,[6] and dehalogenation of aryl halides to arenes.[9]

The selective reduction[12] of α-enones **2** is of interest as this problem is frequently encountered is synthetic schemes. Our previous publications[13] describe their regioselective conversion to

Chart I

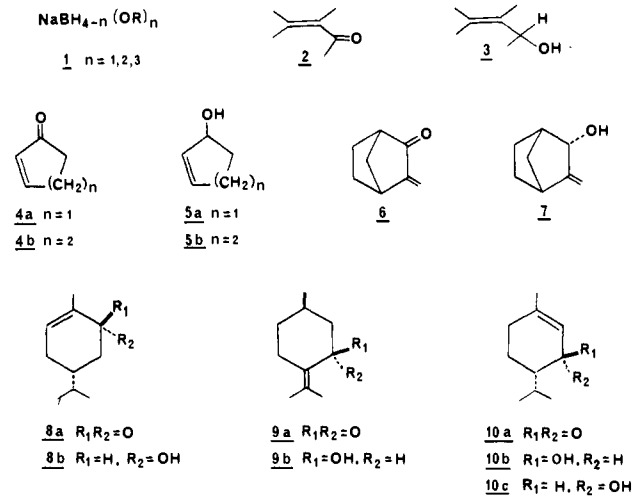

Table I. Reduction of 4a with $NaBH_4$ in MeOH in the Presence of Metallic Salts[a]

	% of product[b]			
ion	4a	5a		
La^{3+}	0	90	0	10
Ce^{3+}	0	97	0	3
Sm^{3+}	0	94	0	6
Eu^{3+}	0	93	0	7
Yb^{3+}	0	89	0	11
Y^{3+}	0	86	0	14
Li^{+}	0	1	0	99
Cu^{+}	2	6	4	88
Ba^{2+}	7	6	11	76
Zn^{2+}	90	trace	7	3
Fe^{2+}	19	12	9	60
Fe^{3+}	33	5	12	50
Tl^{3+}	86	2	8	4
Ni^{2+}	18	0	76	6
Co^{2+}	27	0	61	12

[a] 0.4 M methanol solution; enone, $NaBH_4$, and metallic salt: 1 equiv each, 5 min. [b] GLC measurements (see Experimental Section).

(1) Preceding paper in this series: Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

(2) (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (b) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (c) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. (d) See also the monograph "Sodium borohydride" Thiokol, Ventron division. Danvers, Mass., **1979**.

(3) (a) Lefour, J. M.; Loupy, A., *Tetrahedron* **1978**, *34*, 2597. (b) Perlberger, J. C.; Muller, P. *J. Am. Chem. Soc.* **1977**, *99*, 6316. (c) Dewar, M. J. S.; McKee M. L. *Ibid.* **1978**, *100*, 7499. (d) Huet, J.; Maroni-Barnaud, Y.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, 159. (e) Bottin, J.; Eisenstein, O.; Minot, C.; Anh, N. T. *Tetrahedron Lett.* **1972**, 3015. (f) Loupy, A.; Seyden-Penne, J. *Tetrahedron* **1980**, *36*, 1937.

(4) Inter alia see: Wigfield, D. C.; Gowland, F. W. *Tetrahedron Lett.* **1979**, 2209; *J. Org. Chem.* **1977**, *42*, 1108; *Tetrahedron Lett.* **1976**, 3373 and references cited.

(5) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 2582.

(6) Chung, Sung Kee *J. Org. Chem.* **1979**, *44*, 1014 and references cited.

(7) (a) Fleet, G. W. J.; Fuller, C. J.; Harding, P. J. C. *Tetrahedron Lett.* **1978**, 1437. (b) Sorrell, T. N.; Pearlman, P. S.; *J. Org. Chem.* **1980**, *45*, 3449.

(8) Lin, Shaw Tao; Roth, J. A. *J. Org. Chem.* **1979**, *44*, 309.

(9) Kano, S.; Yuasa, Y.; Shibuya, S. *Chem. Commun.* **1979**, 796.

(10) Subba Rao, B. C., *Curr. Sci.* **1961**, *30*, 218; *Chem. Abstr.* **1961**, *56*, 3326C. Tanaka, Y.; Hibino, S. *Chem. Commun.* **1980**, 415.

(11) Yoon, N. M.; Lee, H. J.; Kang, J.; Chung, J. S. *Taehan Hwahakhoe Chi* **1975**, 468; *Chem. Abstr.* **1976**, *84*, 134703.

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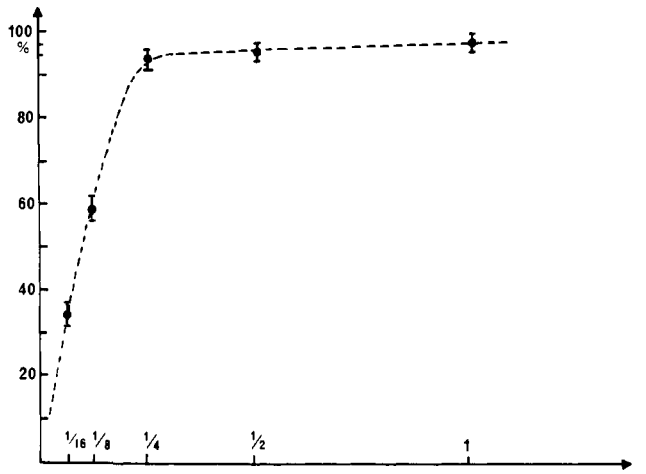


fig. 1

Figure 1. Percent yield of **5a** vs. the number of molar equivalents of $CeCl_3 \cdot 6H_2O$.

allylic alcohols **3**, by $NaBH_4$ in methanol solution, in the presence of lanthanoid derivatives. This procedure, which allows highly regioselective 1,2 reduction, is complementary to those which give predominant 1,4 selectivities with the aid of sodium hydrotelluride[14] or $NaBH_4$ in pyridine.[15] The general utility of the $NaBH_4$–$CeCl_3$ selective reduction is illustrated by the conversion of 2-cyclopentenone (**4a**) to 97% 2-cyclopentenol (**5a**) and only 3% cyclopentanol, although conjugate reduction of cyclopentenone systems by most hydride reagents is usually highly favored. In view of this, we initiated an investigation of the mechanistic and stereochemical aspects of the reaction, the results of which are reported in this article.

Results and Discussion

After much experimentation, the best conditions found for maximum yield and regioselectivity were to employ 1 molar equiv of $NaBH_4$ for each mole of substrate in 0.4 M methanolic $CeCl_3 \cdot 6H_2O$. Many enones were thus converted essentially quantitatively to the allylic alcohol at room temperature.[16]

The nature of the metallic ion was found to be an important factor for the regioselectivity (Table I).

Replacement of the lanthanoid ion by other elements results in a strong decrease of the 1,2 reduction of **4a**. In some cases (Tl^{3+}, Zn^{2+}) complete decomposition of the reducing agent occurs very rapidly and the starting material is recovered as the major component of the mixture. Among the lanthanoids tested, cerium gave the highest selectivity with most enones and is generally recommended. This finding is of interest for economical reasons as cerium is one of the less expensive of the rare earth elements.

For the same reason and for mechanistic studies, we investigated the possibility that Ce^{3+} could function catalytically or, at least, in less than stoichiometric amounts.

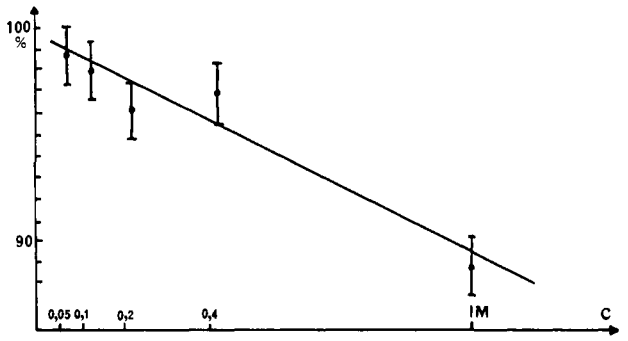


fig. 2

Figure 2. Percent yield of **5a** vs. concentration of **4a** and $CeCl_3 \cdot 6H_2O$.

Table II. Solvent Effect on the Reduction of 4a[a]

solvent	% of conversion[b]	% of selectivity[b] 1,2	1,4
MeOH	100	97	3
MeOH:H_2O (9:1)	100	85	15
MeOH:H_2O (1:1)	100	50	50
EtOH	100	90	10
MeOH:pyridine (4:1)	100	95	5
i-PrOH[c]	80	60	20

[a] 0.4 M solution; $CeCl_3 \cdot 6H_2O$, enone, and $NaBH_4$: 1 equiv each, 5 min. [b] GLC measurements. [c] Due to its insolubility in this solvent, $CeCl_3$ was replaced by erbium chloride.

As shown in Figure 1, the 1,2 selectivity remains high for $[Ce^{3+}]$/[substrate] ratios larger than 0.25, but for lower values, a sharp decrease occurs. The overall concentration in methanol is also an important factor, as shown in Figure 2. A decrease in the concentration of all the reacting species results in a more selective reaction. An extrapolation of the curve to infinite dilution gives a 100% selectivity for the reduction of **4a** to **5a**.

The effect of solvent was also investigated and the results are summarized in Table II. Methanol was found to provide the highest selectivity accompanied by a very high reaction rate. For example, compounds **4a** and **6** were quantitatively reduced to the corresponding allylic alcohols **5** and **7** in ca. 15 s. The selectivity and reaction rate were progressively reduced in ethanol and isopropyl alcohol.

At the onset of this study, we envisioned that the role of the lanthanoid ions was to modify the geometry or electronic density, therefore the reactivity, of the conjugated system. For example, the presence of Eu^{3+} shift reagents can modify the conformation of some flexible ketones.[17] Changes in the regiochemical course of α-enone reactions could also be expected from the presence of Ln^{3+} ions, in analogy with the important effect of alkaline ions on the electron density in the conjugated carbonyl system.[3a] In aprotic solvents, the effect of complexation of the C=O group by Li^+ and Na^+ on the reactivity of enones is well documented.[2c,3,18]

Under the conditions of complexation control, the attack of the conjugate system at carbon 2 is enhanced and the reaction rate is increased.[3a] Conversely, suppression of the complexation control, for instance by the use of a cryptand, was shown to result in an enhanced 1,4 selectivity and a decreased reaction rate.[3f]

That such control exists with lanthanoid ions is illustrated by the reduction of **4a** to **5a** in 95% yield by $NaBH_4$ in an anhydrous THF solution of SmI_3. When compared to the reductions performed in the presence of Li^+ or Na^+, the dramatic selectivity modification is obviously related to the different nature of the added complexing cation.[19]

(12) (a) Krishnamurthy, S.; Brown, H. C., *J. Org. Chem.* **1975**, *410*, 1864. (b) Winterfeldt, E. *Synthesis* **1975**, 617. (c) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530. (d) Johnson, M. R.; Rickborn, b. *J. Org. Chem.* **1970**, *35*, 1041. (e) Lane, C. F., *Aldrichimica Acta* 1976, *9*, 31. (f) Mordenti, L.; Brunet, J. J.; Caubère, P. *J. Org. Chem.* **1979**, *44*, 2203. (g) Loupy, A.; Seyden-Penne, J. *Tetrahedron Lett.* **1978**, 2571. (h) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin, Inc.: Menlo Park, Calif., 1972 2nd ed. (i) Wilson, K. E.; Seidner, R. T.; Masamune, S. *Chem. Commun.* **1970**, 213. (j) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

(13) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J. L., Rodriguez-Hahn, L.; Crabbé, P. *Chem. Commun.* **1978**, 601. Gemal, A. L.; Luche, J. L. *J. Org.* Chem. **1979**, *44*, 4187. It is worth mentioning that in the case of a γ pyrone, the usually difficult 1,4 reduction has been achieved by $NaBH_4$ in a methanolic solution of ceric nitrate. See: Poulton, G. A.; Cyr, T. D. *Synth. Commun.* **1980**, *10*, 581.

(14) Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847.

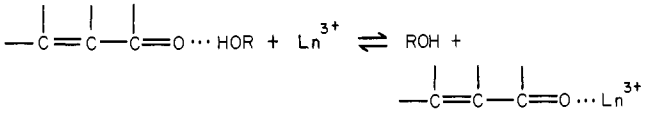
(15) Jackson, W. R.; Zurquiyah, A. *J. Chem. Soc.* **1965**, 5280.

(16) The effect of temperature on the stoichiometry has not been investigated.

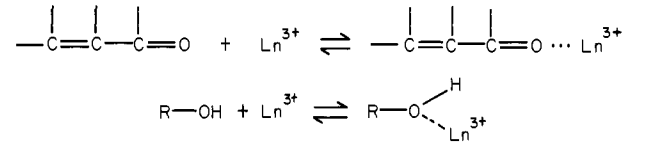
(17) Dunkelblum, E.; Hart, H. *J. Org. Chem.* **1977**, *42*, 3958.

(18) Handel, H.; Pierre, J. L. *Tetrahedron* **1975**, *31*, 2799. Handel, H. Thesis, Grenoble **1978**. See also ref 2c. It is worth noting that the geometries of the C(=O)···Li^+ and C(=O)···Eu^{3+} complexes are closely related; see ref 3a and: Raber, D. J., Janks, C. M.; Johnston, M. D.; Raber, N. K. *J. Am. Chem. Soc.* **1980**, *102*, 6594.

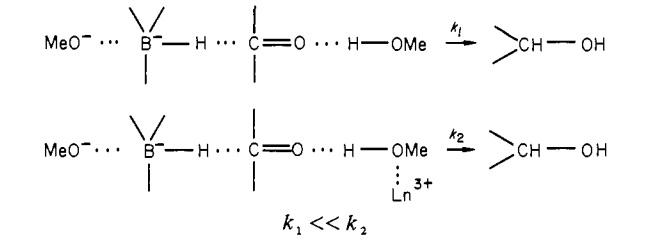
However, most reductions of enones in the presence of Ce^{3+} have been run in methanol, and there is no evidence that in a protic solvent complexation control is still effective. The results obtained by varying the overall concentration of the reaction medium disagree with the preceding explanation. Experimentally, in a methanol solution, the 1,2 regioselectivity is increased by a decrease in concentration. In a dilute solution, the complexation equilibrium is shifted to the left.



The reduction selectivity should then become similar to that observed without Ln^{3+} ions, in opposition to the experimental results. Furthermore, it is known that lanthanoid ions preferentially bind to alcohols rather than to C=O groups as shown by NMR spectroscopy.[20]



Thus, dilution should shift the second equilibrium to the right at the expense of the first, and the effect of the cation on the reduction selectivity should progressively disappear. As the opposite is observed, complexation of the carbonyl is probably not of major importance. Complexation of the solvent by Ln^{3+} is in contrast highly facilitated and should result in a stronger acidity of the medium. This is illustrated by the catalytic role of lanthanoid ions in the ketalization of various aldehydes and ketones.[21] The push–pull type mechanism, with electrophilic assistance by the solvent proposed by Wigfield,[4] should therefore be accelerated by an increase in acidity. In addition, the effect of a hard Lewis acid such as cerium,[22] even if weak, should contribute both to the 1,2 selectivity and the high reaction rate, as observed.



$k_1 << k_2$

Whether the effect is large enough to produce the observed, >90% regioselective reductions is unclear and the problem of the actual reducing species has to be examined. In analogy with known cases (i.e., zinc or copper) lanthanoid borohydrides resulting from a cation exchange were considered as the possible reducing agents. These species have been reported[23] but their reducing properties have not been described. Consequently, several borohydrides such as $LnCl(BH_4)_2$ and $Ln(BH_4)_3$ with Ln = Ce or Sm were prepared[23] and utilized for the reduction of **4b**. In THF solution, the reduction was non-regioselective while in methanol

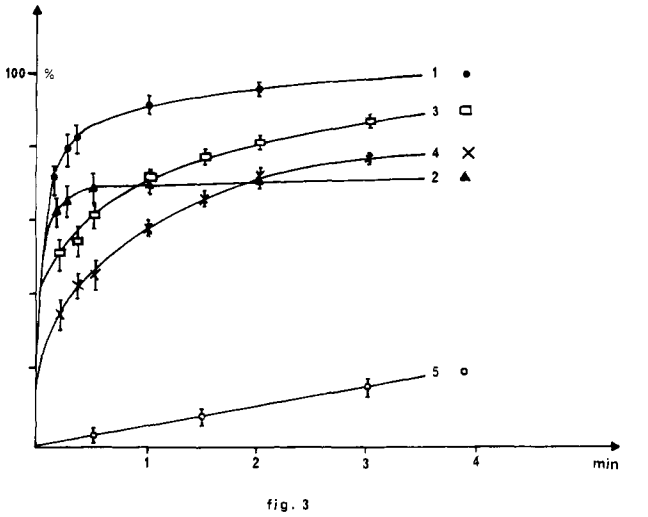


fig. 3

Figure 3. Percentage of the H_2 evolution vs time: (1, ●) $NaBH_4$ + 0.5 equiv of $CeCl_3$ in methanol; (2, ▲) $NaBH_4$ + 0.5 equiv of $CeCl_3$ + 1 equiv of cyclopentenone (**4a**) in methanol; (3, □) $NaBH_4$ + 0.125 equiv of $CeCl_3$ in methanol; (4, ×) $NaBH_4$ + 0.062 equiv of $CeCl_3$ in methanol; (5, ○) $NaBH_4$ in methanol without $CeCl_3$.

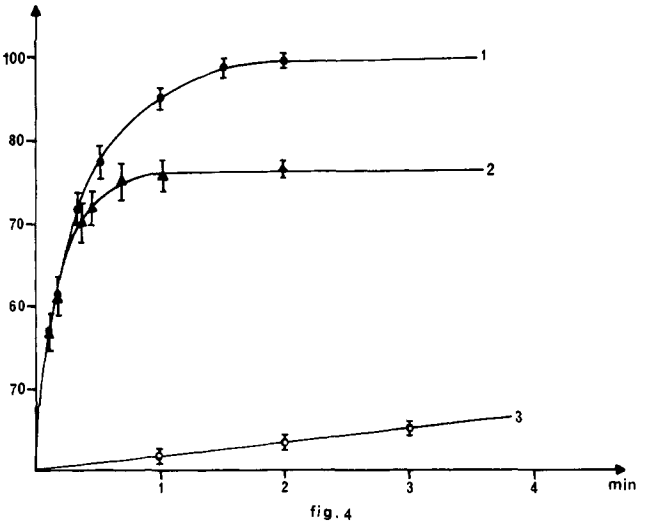


fig. 4

Figure 4. Percentage of H_2 evolution vs. time: (1, ●) $NaBH_4$ + 0.5 equiv of $CeCl_3$ in ethanol; (2, ▲) $NaBH_4$ + 0.5 equiv of $CeCl_3$ + 1 equiv of cyclopentenone (**4**) in ethanol; (3, ○) $NaBH_4$ + 0.5 equiv of $ErCl_3$ in isopropyl alcohol.

destruction of the reagent occurs more readily than reduction of the substrate. A mechanism involving reduction by a transient divalent species Ln^{2+} can be ruled out as these species are highly reactive in the presence of atmospheric oxygen, and they react poorly with ketones.[24]

Under the conditions we employ, 1 molar equiv of $NaBH_4$ (i.e., a 4-fold hydride excess) is required for complete reduction of the enone. A vigorous hydrogen evolution occurs upon mixing of $NaBH_4$ with the methanol solution of the lanthanoid salt. This demonstrates an important catalytic effect of the lanthanoid ions in the MeOH–BH_4^- reaction. This reaction has been extensively studied and shown to involve the formation of alkoxyborohydrides $NaBH_{4-n}(OR)_n$.[25] The first reaction ($NaBH_4$ + ROH → $NaBH_3OR$ + H_2) was demonstrated to be rate determining and the process terminates with the formation of tetraalkoxyborate $NaB(OR)_4$. Several metallic ions have been shown to have

(19) Other examples of this strong complexation effect were investigated. Addition of methylmagnesium iodide to enones thus occurs with an increased 1,2 selectivity in the presence of SmI_3. These results will be discussed in a future paper.

(20) Inter alia see: Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553.

(21) Luche, J. L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.

(22) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533; *J. Chem. Educ.* **1968**, *45*, 581, 643.

(23) (a) Marks, T. J.; Kolb, J. R. *Chem. Rev.* **1977**, *77*, 263. (b) Marks, T. J.; Grynkewich, G. W., *Inorg. Chem.* **1976**, *15*, 1302. (c) Rossmanith, K.; Muckenhuber, E. *Monatsh. Chem.* **1961**, *92*, 600.

(24) Girard, P.; Namy, J. L.; Kagan, H. B. *Nouv. J. Chim.* (**1977**), *1*, 5.

(25) (a) Davies, R. E.; Gottbrath, J. A. *J. Am. Chem. Soc.* (**1962**), *84*, 895. (b) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 1493. (c) Brown, H. C.; Ichikawa, K. *Ibid.* **1961**, *83*, 4372.

Table III. Regioselective Reductions by $NaBH(OCH_3)_3$ under Various Conditions

	1,2:1,4 selectivity			
substrates	in MeOH	in MeOH + $CeCl_3$	in THF	in THF + ErI_3
4a	8:92	93:7	26:74	95:5
4b	50:50	99:1	77:23	93:7

catalytic effects[25] including Cu^{2+}, Mn^{2+}, and cations of the VIIIb column. In our case, the catalytic effect of Ce^{3+} is shown in the kinetic curves representing the hydrogen evolved as a function of time (Figures 3 and 4).

The reaction is very fast in methanol with 0.5 molar equiv of $CeCl_3$ (with respect to $NaBH_4$) and somewhat slower in ethanol: 90% reaction at 40 s in MeOH vs. 60 s in EtOH.[26] In isopropyl alcohol only 10% reaction is reached in ca. 180 s. The same experiments were carried out in the presence of 2-cyclopentenone (1 equiv with respect to $NaBH_4$), and the H_2 evolution is represented by curve 2 (Figure 3). When compared to curve 1, the total gas volume has been reduced by 25%. This factor corresponds to the hydride consumed by the enone reduction. The shape of the curve suggests that this reduction is accomplished very rapidly, as mentioned qualitatively above. Although the initial parts of curves 1 and 2 suffer from some inaccuracy, they cannot be distinguished from each other. Similar observations are made in the experiments performed in ethanol. The Ln^{3+} catalyzed decomposition of BH_4^- by the solvent thus appears to be the rate-determining step. It is therefore highly probable that the actual reducing species is not BH_4^-, but the derived alkoxyborohydrides and the following arguments bring some substance to this statement.

Alkoxyborohydrides and among them the monosubstituted species BH_3OR^- are known[2,27] to be more reactive than BH_4^-, and should be at least in part responsible for the very high reduction rate in the presence of Ce^{3+}. In methanol, a decrease in the overall concentration (Figure 2) should favor the formation of $NaBH_{4-n}(OCH_3)_n$, and BH_4^- is decomposed before reduction of the enone occurs. On the other hand, a decrease in the Ce^{3+} concentration, all the other factors being held constant (Figure 1), lowers the rate of reaction of $NaBH_4$ with methanol and the contribution of the alkoxyborohydrides to the overall selectivity. Reduction of **4** in the presence of Ln^{3+} occurs slowly in isopropyl alcohol and the selectivity is poor. This can be accounted for by the much slower formation of isopropoxyborohydrides $NaBH_{4-n}(O\text{-}i\text{-}Pr)_n$, allowing BH_4^- to react before it is decomposed.

Reductions with trimethoxyborohydride were expected to give some analogies with the results described above and possibly to provide confirmation of the proposed mechanism. The results are given in Table III.

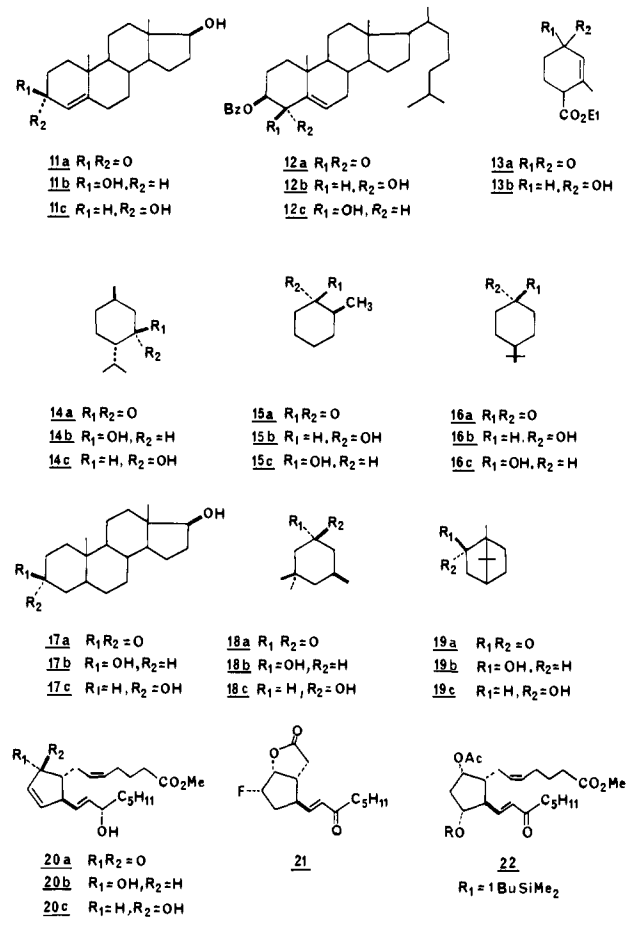
In THF solution, $NaBH(OCH_3)_3$ is stable enough[2] to function as the reducing species. Comparison of the regioselectivities with and without erbium iodide[28] confirms that the complexation effect of the lanthanoid ion on the conjugated system is very important in an aprotic medium, as shown above with SmI_3 in the same solvent. In methanol, the results resemble strongly those obtained with $NaBH_4$. It can then be postulated that without Ce^{3+} the trimethoxy derivative is able to disproportionate, in contrast to the monomethoxy.[2b] With Ce^{3+} present, the parallel observed with $NaBH_4$ and $NaBH(OCH_3)_3$ should also indicate that similar species, i.e., methoxyborohydrides, are involved in the reaction.

(26) In the presence of small amounts of water, the 1,2 selectivity as well as the reduction velocity remain unaffected. Reductions in a 50–50 H_2O–alcohol mixture have not been studied.

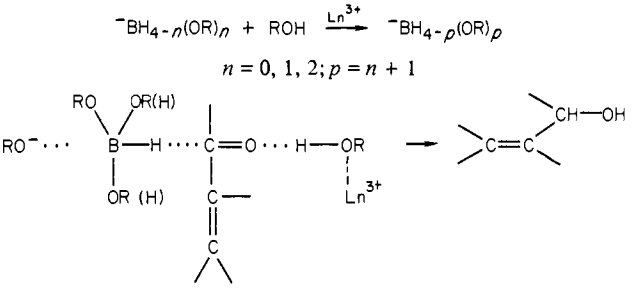
(27) Wuesthoff, M. T. *Tetrahedron* **1973**, *29*, 791. Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.

(28) Cerium chloride is almost insoluble in THF. In this solvent, it was replaced by samarium or erbium iodides.

Chart II



Taking into account the solvent complexation effect discussed above, a reasonable mechanistic interpretation can be formulated as shown below.



Such an interpretation is in good agreement with previous works.[3e] From the hard and soft acids and bases (HSAB) theory, it was deduced that the substitution of hydrides in BH_4^- by alkoxy groups increases the hardness of the reagent. The attack of the conjugate enone system is then enhanced at the hard site, i.e., carbon 2. Ahn[3d] has also suggested that the stereoselectivity of the reduction is related to the hardness of the hydride compound, the harder the reagent, the more favored the axial attack of cyclohexanones. Indeed it was observed that most enone reductions performed in the presence of Ce^{3+} yielded greater preference of the equatorial alcohols as shown in Table IV with compounds **8a**, **9a**, **11a**, **12a**.

Two noticeable exceptions are piperitone (**10a**) and Hagemann's ester, **13a**. For the latter, the presence of Ce^{3+} has no effect on the stereoselectivity, while an inversion occurs with the former. $NaBH_4$ in MeOH, or $LiAlH_4$ in diethyl ether, yield a majority (64% and 69%, respectively) of the equatorial trans alcohol **10b**. In contrast, $NaBH_4$ with $CeCl_3$ in methanol or SmI_3 in THF give rise to a majority (65%) of the cis alcohol **10c**. A modification of the conformational equilibrium of piperitone[29] by Ce^{3+} and the

Table IV. Stereoselectivity of the Reduction of Ketones in Methanol Solution[a]

ketone	% of equatorial alcohol: without $CeCl_3$	% of equatorial alcohol: with $CeCl_3$
carvone (8a)	100[b]	100
pulegone (9a)	69	97
piperitone (10a)	64[c]	35
testosterone (11a)	90[d]	99
12a		99[e]
13a	70	70
menthone	55[f]	82
2-methylcyclohexanone (15a)	69[f]	69
4-*tert*-butylcyclohexanone (16a)	81[g]	94
dihydrotestosterone (17a)	81[h]	>95
dihydroisophorone (18a)	18[g]	51
camphor (19a)	62[i]	68

[a] Figures representing the percentage of equatorial alcohol in the final mixture result from VPC or NMR analysis. Complement to 100% is the axial alcohol. [b] Reduction of 8a by $LiAlH_4$ yields 8b in quantitative yield. See ref 30. [c] Without Ce^{3+}, the cumulative yield of allylic alcohols 10b and 10c is 61%, the remaining 39% being neomenthol (14%) and menthol (25%). [d] See ref 12b. [e] See ref 31. [f] See ref 32. [g] See ref 33. [h] At 65 °C. See ref 34. [i] Exo epimer. 86% of the same alcohol with $NaBH_4$ in *i*-PrOH at 0 °C. See ref 35.

increased steric crowding of the reagent can both be invoked to explain this reversal of stereoselectivity.

For open-chain enones, or cyclopentenones in the prostaglandin series **20–22**, the stereoselectivity proved to be poor. Reduction of **20** gave a 1:1 mixture of the 9α-OH and 9β-OH **Δ10** alcohols. Results with a similar order of magnitude were obtained from **21**[36] and **22**.[37]

In parallel with α-enones, saturated ketones are also attacked on the axial side, with a selectivity enhanced by Ce^{3+}. For example, dihydroisophorone (**18a**) yields a 18:82 ratio of the equatorial:axial alcohols under the usual conditions. With 1 molar equiv of $CeCl_3$ this ratio shifts to 51:49. Two exceptions again were found, camphor and 2-methylcyclohexanone (**15a**). The conformational mobility of the latter ketone, as in the case of **10a**, is one of the possible explanations for the experimental result. That no stereoselectivity change occurs from the presence of Ce^{3+} underscores the complexity of the system[38] but does not conflict with the mechanistic interpretation given in this paper.

Experimental Section

Infrared spectra were taken in $CHCl_3$ solution, or as films for liquids with a Beckman Acculab 4 instrument. UV spectra were obtained with a DBT spectrophotometer. NMR spectra were recorded on a PM X 60 Jeol instrument in $CDCl_3$ with Me_4Si as an internal standard. Resonance frequencies δ are quoted in ppm downfield from Me_4Si. Rotations were taken at 22 °C with a Perkin–Elmer Electronic polarimeter Model 141. GLC analyses were obtained on a Carlo Erba Fractovap chromatograph equipped with a Carbowax 20 M 10% Chromosorb WAW column (2 mm i.d. × 2 m) with a 20 mL/min N_2 flow.

Lanthanoid derivatives and sodium trimethoxyborohydride were used as received from Alfa-Ventron Corp. Sodium borohydride was obtained from Fluka A.G. (Switzerland), or Prolabo.

General Procedure for Reductions. The α-enone and $LnCl_3 \cdot nH_2O$ (1 mmol each) were dissolved in 2.5 mL of methanol. $NaBH_4$ (38 mg, 1 mmol) was added in one portion, with stirring. A vigorous gas evolution occurs, together with a temperature rise (≃35–40 °C). Stirring was continued for a few minutes (3–5 min) before the pH was adjusted to neutrality with dilute aqueous HCl, the mixture was extracted (ether) and dried (Na_2SO_4), and the solvent evaporated. The crude residue was analyzed for quantitative determinations by NMR and/or GLC. It was then purified by column chromatography and identified by the usual spectroscopic methods and comparison with authentic samples.

The same procedure was followed for experiments under various conditions (variation of the concentration, the solvent or the cation, the relative quantities of Ln^{3+} or $NaBH_4$). In experiments with time limitation (e.g., 15 s) quenching of the reaction was done by rapid addition of aqueous NH_4Cl in large excess, followed by the usual workup.

Reduction of Cyclopentenone (4a). From 70 mg (0.84 mmol) of the ketone an oil was obtained (75 mg), consisting of almost pure cyclopentanol (**5a**). IR and NMR spectra agree with published data.[39] The NMR spectrum reveals the presence of 10% MeOH (by weight, i.e., 7.5 mg). VPC under the specified conditions (t = 90 °C) shows two peaks at 5.3 min (3%, cyclopentanol) and 6.3 min (97%, **5a**) identified by comparison with authentic samples. No peak was observed at 2.6 min (cyclopentanone) and 7.6 min (**4a**).

Reduction of 20a.[40] From 280 mg of **20a** there were obtained 300 mg of a crude oil, which was chromatographed on silica gel. Fractions of the pure 9α-OH **20b** (105 mg), a mixture of **20b** and **20c** (58 mg), and the pure 9β-OH **20c** (90 mg) were collected. The total isolated yield was 90%.

9α-OH epimer 20b: yield 38%; IR (film) 3400, 3060, 3020, 1740, 1725, 1660, 1440, 1030, 970, 740 cm^{-1}; NMR ($CDCl_3$) δ 5.7–5.2 (m, 6 H), 4.4 (m, 1 H), 3.9 (m, 1 H), 3.55 (s, 3 H), 2.9 (m, 2 H), 2.5–0.8 (m, 21 H).

9β-OH epimer 20c: yield 32%; IR (film) 3400, 3070, 3020, 1735, 1720, 1660, 1460, 1440, 1000, 970, 740 cm^{-1}; NMR ($CDCl_3$) δ 5.7–5.2 (m, 6 H), 4.2 (m, 1 H), 3.9 (m, 1 H), 3.5 (s, 3 H), 3.2–2.7 (m, 3 H), 2.5–0.8 (m, 20 H).

***cis*-Pulegol (9b).** Following the given procedure, 150 mg (0.98 mmol) of pulegone (**9a**) yielded 150 mg of an oil isolated after the usual workup and evaporation of the solvents at room temperature. Crystallization occurs on standing. Washing with pentane yields crystals with mp 29–30 °C $[\alpha]_D$ – 104° (EtOH, H_2O 95:5, *c* 4) [lit.[41] mp 31.5 °C, $[\alpha]_D$ –107° (EtOH, *c* 1)].

Reduction of Piperitone (10a). From 154 mg (1 mmol) of **10a** an oil (155 mg) was obtained in which VPC shows the presence of 65% cis and 35% trans alcohols. With $LiAlH_4$, *cis*- and *trans*-piperitol are formed in a ratio of 36 and 64%, respectively.[42]

3-Methylenenorborneol (7): IR (film) 3350, 3050, 1650, 1440, 1150, 1100, 1070, 1040, 1020, 880 cm^{-1}; NMR ($CDCl_3$) δ 4.9 (br s, 2 H), 4.3 (m, 1 H), 2.7 (br s, 1 H), 2.3 (br s, 1 H), 2.0 (s, 1 H), 2.0–1.0 (m, 6 H). VPC analysis (Carbowax 20M, 15 mL N_2/min, 130 °C) reveals a single peak, which could not be resolved. Reduction by $NaBH_4$ in $MeOH \cdot H_2O$ of **6** is known to give mostly the endo alcohol.[43]

Reduction of 13a. From 346 mg (ca. 2 mmol) of **13a** the allylic alcohol **13b** was obtained in 94% yield (326 mg). The epimeric composition of the mixture was obtained by NMR in the presence of $Eu(dpm)_3$.

Preparation of $CeCl(BH_4)_2$. Anhydrous $CeCl_3$ (2.46 g, 10 mmol) and 0.5 g of $LiBH_4$ (22 mmol) are placed in a flask under a dry nitrogen atmosphere. Dry THF (60 mL) is slowly added and an exothermic reaction takes place. The heterogeneous mixture is stirred for 30 min and then filtrated on a sintered glass funnel under a nitrogen blanket. The precipitate was washed with benzene and the filtrate evaporated. Dry benzene (150 mL) was added to the residue and the solution was evaporated to reduce the volume to 50 mL. Lithium chloride separated and the supernatant was used in the reductions. The procedure was also used for the preparation of $SmCl(BH_4)_2$ and $ErCl(BH_4)_2$.

Preparation of $Ce(BH_4)_3$. Anhydrous $CeCl_3$ (1.24 g, 5 mmol) in 15 mL of dry methanol was treated with 15 mmol (7 mL) of sodium

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methoxide in methanol solution (obtained from 0.5 g of Na and 10 mL of methanol). This addition was followed by 5 mL of THF and 6 mL of a 1 M solution of BH_3 in THF. After being stirred overnight at room temperature, the solvent was distilled off and the residue dissolved in 25 mL of benzene. Sodium chloride was decanted and the supernatant used for the reductions.

Reductions with Lanthanoid Tetrahydroborates. The keto compound (1 mmol) in 1 mL of THF or methanol under a nitrogen atmosphere was treated by 3 to 5 mL of the reagent solution, stirred for 5–30 min at room temperature, and then hydrolyzed, worked-up as usual, and analyzed by VPC. For example, in THF solution cyclohexenone yields 80% cyclohexanol and 20% cyclohexenol. Norcamphor gives 80% of the endo alcohol and 20 of the exo alcohol.

Methanolysis of $NaBH_4$ in the Presence of $CeCl_3$. A two-necked round-bottom flask (50 mL) was equipped with a magnetic stirring bar, a 20 mL equalized pressure dropping funnel, and a tube connected to a graduated cylinder filled with saturated aqueous NaCl. $NaBH_4$ (20 mg) is placed in the flask and 10 mL of a methanol solution of $CeCl_3$ in the funnel. The expected total H_2 volume is 47 mL. At t_0, the solution is added onto $NaBH_4$ with vigorous stirring. The gas volume evolved is measured by a direct reading. The estimated error is ca. 5 mL for rapid evolutions and 0.5 mL for slow evolutions. Reproducibility was found under the error limits and the curves result from at least three measurements.

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Synthesis of Halo Enol Lactones. Mechanism-Based Inactivators of Serine Proteases[1]

Grant A. Krafft and John A. Katzenellenbogen*

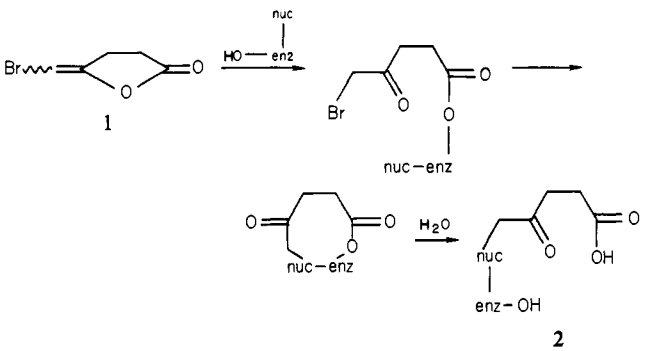
Contribution from the Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received January 19, 1981*

Abstract: Enol lactones bearing a halogen at the vinylic position are potential mechanism-based inactivators (suicide inactivators) of serine hydrolases, since acyl transfer to the active-site serine releases an α-halo ketone that can react with nucleophilic sites in the active-site region. Efficient syntheses of such halo enol lactones needed for enzymatic studies are described. 5-Hexynoic acids can be cyclized with mercuric ion catalysis to γ-methylene butyrolactones. Cyclization of the 6-bromo and 6-chloro analogs leads stereospecifically to the *Z*-halo enol lactones (trans addition), but is quite slow. Cyclization of unsubstituted or 6-methyl- or 6-trimethylsilyl-substituted 5-hexynoic acids is more rapid, but olefin isomerization occurs during the reaction. Direct halogenation of γ-methylene butyrolactones leads to preferential elimination in an endocyclic sense, producing the undesired 5-bromomethylidene-2(3*H*)-furanones; however, the 5-trimethylsilylmethylene and the 5-mercuriomethylene butyrolactones can be converted with moderate efficiency into the desired 5-bromomethylene butyrolactones. The most efficient approach is direct halolactonization of the 5-hexynoic acids with bromine or iodine in a two-phase system with phase-transfer catalysis. This method was used to prepare various 5-halomethylene or 5-haloethylidene 2-phenylbutyrolactones and 6-bromo- and iodomethylene valerolactones. In certain cases where undesired enolization is blocked, γ-halomethylene butyrolactones can be prepared by cyclization of α-halo keto acids (e.g., *o*-(bromomacetyl)benzoic acid to 5-bromomethylidenebenzo-2(5*H*)-furanone), and certain endocyclic halo enol lactones can be prepared by Baeyer–Villiger oxidation of cyclic 3-halo 2-enones. Preliminary studies indicate that these halo enol lactones have reasonable hydrolytic stability, and, in studies presented elsewhere, selected compounds have been found to be efficient inactivators of chymotrypsin.

Introduction

Significant attention in recent years has been focused on mechanism-based enzyme inactivators, also known as suicide substrates.[2] Utilizing its catalytic machinery, the targeted enzyme plays the essential role of unmasking a latent reactive functional group contained in the suicide substrate molecule, revealing a reactive electrophilic species for alkylation of the enzyme. The potential for generating reactive species exclusively within the active site of the enzyme imparts a much higher degree of selectivity of these inactivators than that exhibited by conventional affinity reagents. Thus, suicide inactivators have found utility in in vitro enzyme studies and in in vivo biochemical investigations,[3] and several have shown promise as clinically useful drugs.[4]

Scheme I



2

In 1974, Rando[5] proposed that halo enol lactones such as **1**, which on hydrolysis form α-halo ketones (Scheme I), might function as suicide inactivators for serine proteases and estereases, by reaction with proximal active-site nucleophiles, ultimately forming the modified (inactivated) enzyme **2**. This has prompted us to develop efficient synthetic routes to **1** and to related structures

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