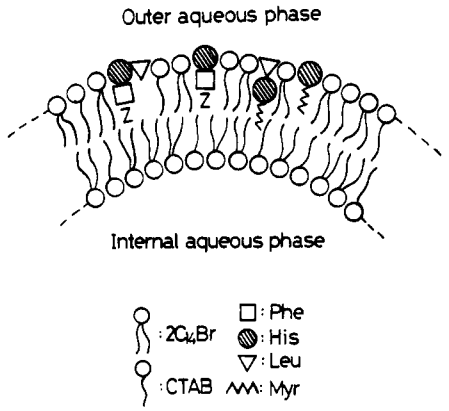

Figure 4. Schematic representation of molecular location of reactants in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB.

tropy of activation, that is, $\bar{T}$ (303 K) exceeded β (287 K). On the other hand, the hydrolysis in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB may be governed by the enthalpy of activation, that is, β (384–443 K) exceeded $\bar{T}$ (296 K). These results suggest that the hydrophobic microenvironment of the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB might be softer than that of the pure $2C_{14}Br$ vesicles.

Furthermore, interestingly, the correlation between β and $\bar{T}$ was $\beta > \bar{T}$ and $\beta \gg \bar{T}$ for the catalytic system of MyrHisLeu and the others (Z-PheHisLeu, Z-PheHis, and MyrHis), respectively. This difference in β values between the catalysts of MyrHisLeu and the others would be attributed to the difference in the location of a His unit (an active site) in the catalysts. The location of catalysts including a His unit in the coaggregates can be drawn schematically as shown in Figure 4. It is deduced that the location of a His unit in MyrHisLeu would be deeper from the surface of coaggregates than that in Z-PheHisLeu, Z-PheHis, or MyrHis. Thus, the first examples of physicochemical discrimination of the molecular location in the reaction field on the basis of isokinetic parameters were proposed.

In conclusion, (a) the pronounced maximum of enantioselectivity was attained at T_c for the hydrolysis of the long-chain substrates (D(L)-S_{12}) in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB; (b) on the basis of the β value, the hydrophobic microenvironment of coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB was suggested to be fairly soft, and furthermore, the location of a His unit in the catalysts employed could be established to depend on the catalysts' frameworks.

Experimental Section

Materials. *p*-Nitrophenyl *N*-(benzyloxycarbonyl)-D(L)-phenylalaninate (D(L)-ZS (**1a**)), *p*-nitrophenyl *N*-dodecanoyl-D-(L)-phenylalaninate (D(L)-S_{12} (**1b**)), *N*-tetradecanoyl-L-histidyl-L-leucine (MyrHisLeu (**3a**)), *N*-tetradecanoyl-L-histidine (MyrHis (**3b**)), and ditetradecyldimethylammonium bromide ($2C_{14}Br$ (**4**)) were prepared by the reported procedure.[8] *N*-(Benzyloxycarbonyl)-L-phenylalanyl-L-histidine (Z-PheHis (**2b**)) was prepared by reactions of *N*-hydroxysuccinimide esters of *N*-(benzyloxycarbonyl)-L-phenylalanine with histidine.[13] *N*-(Benzyloxycarbonyl)-L-phenylalanyl-L-histidyl-L-leucine (Z-PheHisLeu (**2a**)) was obtained from Bachem and was used without purification. Commercially available hexadecyltrimethylammonium bromide (CTAB (**5**)) was recrystallized from an anhydrous ethanol–ether mixture.

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Kinetic Measurements. Rates of *p*-nitrophenol liberation from *p*-nitrophenyl esters were measured at 400 nm with a Hitachi 150-20 UV spectrophotometer. The reaction obeyed the usual pseudo-first-order rate law, and the apparent second-order rate constant ($k_{a,obsd}$) for the hydrolysis of an ester substrate was evaluated by eq 3. where k_t and k_s refer, respectively, to the

$$k_{a,obsd} = (k_t - k_s)/[\text{nucleophile}]_0 \quad (3)$$

oberved first-order rate constants for the hydrolytic cleavage (hydrolysis) of D(L)-ZS and D(L)-S_{12} with and without an nucleophile and $[\text{nucleophile}]_0$ indicates the initial nucleophile concentration.

The clear stock solutions were prepared by dissolving both nucleophile and surfactant in Tris-KCl buffer with sonication (Braun Sonic Model B 3200 apparatus, 90 W) at 50 °C for 1 h.

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Use of Zinc Borohydride as an Efficient and Highly Selective Reducing Agent. Selective Reduction of Ketones and Conjugated Aldehydes over Conjugated Enones

Dipak C. Sarkar, Asish R. Das, and Brindaban C. Ranu*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India

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Selective reduction of one carbonyl group in the presence of other such groups with a minimum of damage to the sensitive portions of a molecule is an important synthetic operation.[1] This frequent requirement has stimulated considerable interest, leading to the development of new reagents and new methods for such selective reductions.[2] The selectivity is generally achieved by the use of modified hydride reagents which are formed by the replacement of hydride with sterically bulky substituents or electron-withdrawing groups in order to discriminate between the structural or electronic environments of the carbonyl groups.[1,2] We describe herein a convenient and efficient methodology for the selective reduction of saturated ketones and conjugated aldehydes over conjugated enones using zinc borohydride without any modification. Although zinc borohydride has been used for the specific reduction of carbonyl groups in a number of cases,[3] to the

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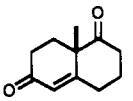
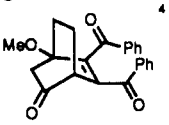
Table I. Reduction of Carbonyl Compounds with Zinc Borohydride

entry	starting carbonyl compound	temp, °C	time, min	% reduction[a]
1	cyclopentanone	−15	30	100
2	3-methylcyclopent-2-en-1-one	−15	30	0
3	3-methylcyclohexanone	−15	30	100
4	3-methylcyclohex-2-en-1-one	−15	30	0
5	cyclohexanone	−78	5	100
6	cyclohex-2-en-1-one	−78	5	14
7	cycloheptanone	−15	30	100
8	7-methoxy-1-benzosuberone	−15	30	0
9	2-chlorocyclohexanone	−15	15	100
10	ethyl 2-oxacyclopentanecarboxylate	30	75	100 (ketone)
11	ethyl acetoacetate	0	120	100 (ketone)
12		−78	30	100 (ketone) 0 (enone)
13		−15	30	100 (ketone) 0 (enone)
14	$PhCH{=}CHCHO$	−15	15	100
15	$PhCH{=}CHCOCH_3$	−15	15	0
16	PhCHO	−78	12	100
17	$PhCOCH_3$	−78	12	15
18	$(Me)_2C{=}CHCH_2CH_2C(Me){=}CHCHO$ (citral)	−78	15	100
19	$(Me)_2C{=}CHCH_2CH_2C(Me){=}CHCOCH_3$	−78	15	0

[a] % Reduction as calculated by ^1H NMR (200 MHz) integration of characteristic peaks.

best of our knowledge no systematic study demonstrating this type of selective reduction has been reported.

In a typical procedure, the carbonyl compound was treated with zinc borohydride in 1,2-dimethoxyethane for a certain period of time (Table I), and the product was isolated in a pure state by simple ether extraction. The results are summarized in Table I.

As shown in Table I, saturated ketones (entries 1, 3, 5, 7) underwent clean and complete reduction, whereas under identical reaction conditions the corresponding conjugated enones (entries 2, 4, 6, 8) remained largely inert.[5] An excellent selectivity was also observed in the reduction of ketones over enones in an experiment with a 1:1 mixture of ketone and enone[6] and in the compounds where both ketone and enone were present in the same molecule (entries 12, 13). Zinc borohydride was also very effective for the reduction of ketone functionalities without damage to sensitive groups such as chloro, methoxy, and carboxylic ester which were present in the molecule (entries 9, 10, 11, 13). Conjugated aldehydes were reduced to allylic alcohols without any observable 1,4-addition much faster than the corresponding methyl ketones were (entries 14–19).

In an earlier report,[3l] zinc borohydride–DMF complex was found to reduce cyclohexanone completely, whereas cyclohexenone remained intact, but no generalized study has been carried out. Recently, a methodology[2a] using sodium borohydride in methanol and dichloromethane, or using acetic acid as catalyst, has become generally accepted for this type of selective reduction. However, the method of using protic solvent or acid in the reaction medium is often not useful for molecules containing acid-sensitive or easily solvolyzable functionalities.[7] The present method, using zinc borohydride in DME, lacks this limitation. Moreover, the compatability of this reagent with a variety of normally reducible functional groups makes it more useful and general than conventional reagents.

In conclusion, the mild reaction conditions, convenience, high yield of reduced product, and absence of side products, coupled with the superior and controllable selectivity recommend this reagent for the facile reduction of ketone functionalities in a molecule that would not tolerate harsher reagents. Particularly noteworthy is the selective reduction of nonconjugated ketones and conjugated aldehydes in the presence of conjugated enones, when this is required in a synthetic operation.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Model 298 spectrometer, and ^1H NMR spectra were recorded on EM 360 and XL 200 spectrometers of Varian Associates in CCl_4 and $CDCl_3$ solutions with Me_4Si as internal standard. Thin-layer chromatography was done on precoated silica gel plates (Eastman Kodak Co.). Ether refers to diethyl ether. Zinc borohydride in 1,2-dimethoxyethane (DME) was prepared from zinc chloride and sodium borohydride according to the reported procedure.[3c]

General Procedure for Reduction. A solution of zinc borohydride (1 mmol) in DME[8] was added to the carbonyl compound

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(5) The use of zinc borohydride to reduce a conjugated ketone to the allylic alcohol under different reaction conditions was reported both by Crabbé[3b,c] and Corey[3m] in the synthesis of prostaglandins.

(6) When a mixture of 1:1 cyclopentanone and 3-methylcyclopentenone was treated with zinc borohydride in DME at −15 °C, 3-methylcyclopentenone was recovered unchanged whereas cyclopentanone furnished cyclopentanol quantitatively. Similar observation was also made in the case of 3-methylcyclohexanone and 3-methylcyclohexenone.

(7) Transesterification or hydrolysis of carboxylic esters while reducing keto esters in methanol or ethanol is one of the common side reactions.

(1 mmol) in DME (2 ml) with stirring usually at −15 °C (ice–salt bath) or as indicated in Table I. The reaction mixture was stirred at that temperature for a certain period of time (Table I) as required for completion (monitored by TLC) and quenched with careful dropwise addition of aqueous hydrochloric acid (0.5 N). The organic phase was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic phase and ether extract was washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated to leave the product, which was identified by comparison with an authentic sample (TLC, IR, and ^1H NMR). In general, the yield was nearly quantitative, and the product did not need further purification.

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Registry No. Cyclopentanone, 120-92-3; 3-methylcyclopent-2-en-1-one, 2758-18-1; 3-methylcyclohexanone, 591-24-2; 3-methylcyclohex-2-en-1-one, 1193-18-6; cyclohexanone, 108-94-1; cyclohex-2-en-1-one, 930-68-7; cycloheptanone, 502-42-1; 7-methoxy-1-benzosuberone, 6500-65-8; 2-chlorocyclohexanone, 822-87-7; ethyl 2-oxacyclopentanecarboxylate, 611-10-9; ethyl acetoacetate, 141-97-9; 3,4,8,8a-tetrahydro-8a-methyl-1,6-(2*H*,7*H*)-naphthalenedione, 20007-72-1; 5,6-dibenzoyl-4-methoxybicyclo[2.2.2]oct-5-en-2-one, 93621-14-8; cyclopentenone, 96-41-3; zinc borohydride, 17611-70-0; 3-methylcyclohexanol, 591-23-1; cyclohexanol, 108-93-0; cyclohex-2-en-1-ol, 822-67-3; cycloheptanol, 502-41-0; 2-chlorocyclohexanol, 1561-86-0; ethyl 2-oxacyclopentanecarboxylate, 54972-10-0; ethyl 3-hydroxybutanoate, 5405-41-4; 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3*H*)-naphthalenone, 4242-00-6; 5,6-dibenzoyl-4-methoxybicyclo[2.2.2]oct-5-en-2-ol, 129467-74-9; PhCH=CHCHO, 104-55-2; PhCH=CHCOCH$_3$, 122-57-6; PhCHO, 100-52-7; PhCOCH$_3$, 98-86-2; Me$_2$C=CHCH$_2$C(Me)=CHCHO, 5392-40-5; Me$_2$C=CHCH$_2$CH$_2$C(Me)=CHCOCH$_3$, 817-88-9; PhCH=CHCH$_2$OH, 104-54-1; PhCH$_2$OH, 100-51-6; PhCH$_2$OHCH$_3$, 98-85-1; Me$_2$C=CHCH$_2$CH$_2$C(Me)=CHCH$_2$OH, 624-15-7.

(8) A stock solution of zinc borohydride in DME, prepared according to the reported procedure (ref 3c), can be stored in a refrigerator in a closed container for several weeks.

Facile Elimination of Nitrous Acid from Quaternary Nitroalkanes[1]

Claus D. Weis and George R. Newkome*

Center for Molecular Design and Recognition, Department of Chemistry, University of South Florida, Tampa, Florida 33620

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The recent resurgence of the chemistry of nitroalkanes has largely dealt with their reactivity toward nucleophiles;[2] in particular, the new synthetic approaches have utilized the single-electron-transfer (SET) mechanism.[3] Attention has also been devoted to $S_{RN}1$ reactions of nucleophiles with α-substituted nitroalkanes; however, with excess base, nitroalkanes eliminated HNO_2 to afford the corresponding α,β-unsaturated derivatives. Recently, facile elimination of HNO_2 from an angular tertiary nitro group upon contact with silica gel or neutral alumina at ambient temperature has been reported.[4]

In our quest for functionalized methane derivatives suitable for the construction of all carbon unimolecular micelles,[5] convenient starting materials were the tertiary nitro triesters, obtained from the base-catalyzed addition of nitromethane to alkyl acrylates. Although syntheses of these triesters have generally been performed in modest yields, using sodium or potassium hydroxide[6] or sodium methoxide in *tert*-butyl alcohol,[7] and in improved yields using liquid ammonia[8] or ion exchange resins,[9] they have generally been plagued with eratic exothermicity. We herein report the preparation of these triesters in 95% yield when the reaction is conducted in the presence of 40% aqueous Triton-B using dimethoxyethane as solvent. The nitro triesters were isolated in >98% purity and were uncontaminated with either the mono- or diester precursors. Saponification of **1a** afforded $O_2NC(CH_2CH_2CO_2H)_3$, which represents an alternative method to using the tris nitrile.[1] These esters are also important starting materials in the preparation of oxo-2,2-pyrrolidinepropionates, as well as a series of novel polymers.[10]

$$O_2NCH_3 + 3CH_2{=}CHCO_2R \rightarrow \underset{\mathbf{1}}{O_2NC(CH_2CH_2CO_2R)_3}$$

Attempts to distill these triesters **1**, as reported,[6] at 10^{-2} mmHg gave rise to partial decomposition with the slow evolution of a reddish gas; only **1a** could be purified by distillation (10^{-3} mmHg) without substantial decomposition. Analytically pure samples of **1** were obtained by flash chromatography on silica gel, without decomposition.

Esters **1** were subjected to thermolysis (305–310 °C) for 12–15 min under an inert atmosphere to probe this degradation, rapid extrusion of HNO_2, in the form of nitrous oxide(s) and water, was observed under these conditions. Although some resinification was observed, the β,γ-unsaturated esters **2** were obtained in 62–65% yield. The

$$\underset{\mathbf{1}}{O_2NC(CH_2CH_2CO_2R)_3} \rightarrow \underset{\mathbf{2}}{(RO_2CCH_2CH_2)_2C{=}CHCH_2CO_2R}$$

a (R = Me), **b** (R = Et), **c** (R = *n*-Bu)

elimination process could be monitored by the disappearance of the prominent absorption (1537 cm^{-1}) for the nitro group in the IR spectrum. The ^1H NMR data for **2** shows a doublet at δ ca. 3.1 for the α-CH_2 triplet at δ ca. 5.4 for the =C*H* indicative of the β,γ-double bond; no evidence of double-bond migration was observed.

4-Nitro-4-(3-hydroxypropyl)-1,7-dihydroxyheptane[1] when treated with acetic anhydride in pyridine afforded (92%) the nitro triacetate **3**, which was confirmed (^1H NMR) by the singlet at δ 1.99 for the acetate methyl. Under similar thermolysis conditions, **3** extruded HNO_2 to generate (67%) the desired trisubtituted olefin **4**, which possessed three unique acetyl methyl groups.

The facile preparation of **1**, which circumvents the well-known detrimental exothermicity in this Michael

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