A Surprising Observation Concerning Sodium Hydride Based Complex Reducing Agents

Åke Nordahl and Rolf Carlson

Department of Organic Chemistry, Umeå University, S-901 87 Umeå, Sweden

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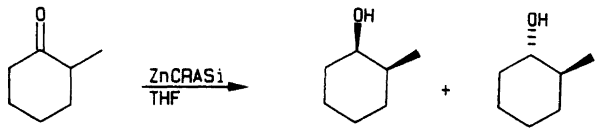
The effects of varying the constituent ratios in sodium hydride – alkoxide – zinc chloride – trimethylsilyl chloride complex reducing agents (CRA) on the stereochemical outcome of the reduction of 2-methylcyclohexanone have been studied. Both factorial and fractional factorial experimental design have been employed for this purpose. This led to the surprising discovery that very active reagents were obtained if the alkoxide was excluded from the mixture. A simple procedure for reagent preparation is described and preparative scale reductions of eight ketones and an aldehyde are demonstrated.

During the last 15 years, Caubere *et al.* have studied sodium hydride based reagents in different types of reductions.[1–6] A few reports on related subjects, from other research groups, have also appeared.[7]

The reagents, abbreviated CRA, are prepared from sodium hydride, an alkoxide and a transition metal salt. The most useful transition metals are nickel (which gives NiCRA) and zinc (which gives ZnCRA). The results of Caubere *et al.* indicate that NiCRA preferentially reduces carbon–carbon double bonds, while ZnCRA shows a preference for the reduction of carbonyl groups.[6] Besides the reactions mentioned above, reduction of aliphatic and aromatic halides, reduction of epoxides, selective reduction of triple bonds, atmospheric pressure carbonylation reactions and coupling of aromatic and vinylic halides, employing different types of CRAs or reagents derived from CRAs, have been reported. Since the structures of the complex reducing agents have not yet been settled, mechanistic details of these reductions remain obscure.

Recently, it was discovered that addition of trimethylsilyl chloride (TMSCl) to the CRAs drastically increased their reactivity, both for the reduction of carbonyl groups[2] and for the reduction of carbon–carbon double bonds.[3] The reagents so obtained are abbreviated as MeCRASi.

One recent paper treats the stereochemistry of reduction of substituted cyclic ketones with MeCRASi. The effect of changing the transition metal in MeCRASis was studied.[4] It appeared to us that not only the nature of the transition metal, but also the proportions of the constituents could have an influence on the stereochemistry. This prompted us to undertake a systematic study, using multivariate methods, of the role of the reagent composition on the stereochemical outcome of the reduction. These studies led to an unexpected observation of the composition fo the reagents. This paper summarizes our findings in this respect.



Scheme 1.

Stereochemical study. As a model reaction we chose the reduction of 2-methylcyclohexanone (Scheme 1) which has been reported to give the corresponding alcohol with poor diastereomeric excess.[4] Any improvement of this would be of preparative interest. As the reducing agent we chose ZnCRASi, which has been shown to be the most efficient for reduction of carbonyl compounds. In general, it also gives high yields.

To analyse whether or not the composition of the reagent has any influence on the stereochemistry of the reaction, we ran experiments in which the relative proportions of the four constituents were used as experimental variables, Table 1. We also included the reaction temperature as an experimental variable. In the first series of experiments we decided to use the same temperature both for preparing the

Table 1. Variables and levels in the experimental design.

Variable	Level		
	–	0	+
x_1: Ratio of sodium hydride:substrate /mol:mol	2		4
x_2: Ratio of alkoxide:substrate/mol:mol	1	1.5	2
x_3: Ratio of zinc chloride:substrate /mol:mol	1	1.5	2
x_4: Ratio of TMSCl:substrate/mol:mol	1	2	3
x_5: Temperature	23 °C		Reflux

Table 2. Design and result of the screening experiment.

Entry	Variable					*cis/trans* isomer ratio
	x_1	x_2	x_3	x_4	x_5	
1	−	−	−	−	+	53/47
2	+	−	−	+	+	33/67
3	−	+	−	+	−	42/58
4	+	+	−	−	−	80/20[a]
5	−	−	+	+	−	34/66
6	+	−	+	−	−	42/58
7	−	+	+	−	+	54/46
8	+	+	+	+	+	37/63

[a]Very slow and incomplete reaction.

reagents and for running the reaction. With this approach we cannot determine in *which* step the temperature is critical, but if it is found that temperature control is significant, experiments to discern its role can easily be carried out. The reaction between *tert*-amyl alcohol and sodium hydride is rather slow. However, after two hours of stirring of the reagent mixture, no remaining *tert*-amyl alcohol could be detected by GC analysis. Reagents prepared with 24 h of stirring did not differ significantly in reactivity or stereochemical outcome. We therefore refer to the introduced alcohol as alkoxide throughout the paper.

In the first run the five variables were investigated by a two-level fractional (2^{5-2}) factorial design,[8] Table 2. In the second run, the variables found to have a significant influence on the stereochemical outcome (Table 4) were then examined in a complete two-level factorial design (Table 3). This was done to determine possible interaction effects between variables. The same levels for the variables as given in Table 1 were used in both designs.

Results

The results of the initial screening experiments and the calculated effects of the variables are found in Tables 2 and

Table 3. Design and results of factorial design.

Entry	Variable			Ratio *cis/trans*	Rate rank
	x_2	x_3	x_4		
1	−	−	−	50/50	7
2	+	−	−	69/31[a]	8
3	−	+	−	39/61	1
4	+	+	−	50/50	6
5	−	−	+	40/60	1
6	+	−	+	48/52	5
7	−	+	+	36/64	1
8	+	+	+	38/62	1
9	0	0	0	46/54	
10	0	0	0	47/53	
11	0	0	0	45/55	
12	−3	1	1	31/69	

[a]Very slow and incomplete reaction.

Table 4. Calculated effects of variables.

Effects[a]	Estimated value		
	Fractional design[b]	Complete design[b]	Rate
b_0	46.88	46.25	3.75
b_1	1.12		
b_2	6.38	5.00	1.25
b_3	−5.12	−5.50	−1.50
b_4	−10.38	−5.75	−1.75
b_5	−2.62		
b_{23}		−1.75	0.00
b_{24}		−2.50	−0.25
b_{34}		2.00	0.50

[a]The functional dependence [$y = f(x_1{-}x_5)$] between the response, y, and the experimental variables, $x_1{-}x_5$, is approximated by a truncated Taylor expansion:

$$y = b_0 + b_1x_1 + \ldots + b_nx_n + b_{12}x_1x_2 + \ldots + b_{(n-1)n}x_{(n-1)}x_n.$$

The effects are the least-squares estimates of the coefficients of the Taylor expansion. In the screening experiments, only linear terms were included. In the factorial experiment, rectangular (cross-product) terms were also included. [b]Effects calculated with percentage *cis* isomer as a response variable.

4. Two variables (amount of sodium hydride and temperature) were found to have only a minor influence on the stereochemical outcome of the reduction. For the next series of experiments they were fixed at suitable levels: reactions with low levels of sodium hydride proceeded more slowly than reactions with high levels of sodium hydride so we decided to use the high level for sodium hydride. The temperature seemed (as might be expected) to influence the reaction rate in a way similar to that of sodium hydride concentration. However, the experimental procedure is simpler if the reactions are run at room temperature. For the sake of convenience, the temperature was fixed at a low level.

The results of the experiments are given in Table 3, and the main effects and two-factor interaction effects were calculated. These are given in Table 4. As can be seen, the interaction effects are small compared with the main effects.

No actual rate measurements were carried out, but by regular sampling of the reactions, a qualitative rate scale could be established, where the fastest reaction was given rank 1 and the slowest was given rank 8. In cases where no dsitinction between reactions could be made by this crude method, the reactions were assigned the same rank. With this qualitative rate scale as the response variable, the effect on the reaction rate of the experimental variables could be estimated (Table 4). It can be seen that if the stereochemical model is extrapolated to predict further improvement in the excess of the *trans* isomer, the rate model predicts an increased reaction rate.

Experiments 9–11 (centre points) in Table 4 were run to check the reproducibility. The standard deviation in these three replicates is 1 %. That is approximately the same as

the standard deviation of the analysis. Recalculation of the model including experiments 9–11 gave, within the limits of error, a result identical with that obtained without the centre points. This indicates that the curvature of the response surface is not significant and it is not necessary to adopt a second-order model with squared terms.

Experiment 12 in Table 4 was based upon an extrapolation from the model. It was run to determine whether it would be possible to increase further the stereoisomeric excess. However, when the model is extraplated to a −3 level for the amount of alkoxide, a peculiar situation occurs. This corresponds to complete exclusion of alkoxide from the reaction mixture. Caubere *et al.*[5,6] have shown that, with only a few exceptions, the presence of alkoxide is necessary for obtaining reagents with reducing properties towards ketones. The result of experiment 12 in Table 4 was therefore surprising. The excess of the *trans*-isomer was further improved and the reaction proceeded very rapidly. It should, however, be mentioned that further experiments have shown that the reproducibility of the stereoisomeric outcome with this reagent combination is not as good as in experiments 9–11.

Control experiments showed that sodium hydride alone did not reduce 2-methylcyclohexanone. When it was combined with zinc chloride reduction took place, but the reaction was slow. Sodium hydride and TMSCl did not give a reaction.

In other control experiments we have studied the effect of varying the time taken to mix the reagents prior to substrate introduction. We have also studied whether or not it is necessary to take careful precautions to exclude moisture from the reaction mixtures. No significant differences in reactivity or yield could be detected when different procedures were used.

The general applicability of this modified reagent and its simplified preparation procedure was checked in preparative-scale reactions. The overall yields were excellent and reaction times were short for unhindered substrates. The results of the preparative runs are given in Table 5.

Table 5. Preparative reactions.[a]

Carbonyl compound[b]		Reaction time/min	Yield[c] (%)
2-Methylcyclohexanone	(1)	6	91
Cyclohexylphenylmethanone	(2)	90	98
2,4-Dimethyl-3-pentanone	(3)	14	92
2-*tert*-Butylcyclohexanone	(4)	480	97[d]
Acetophenone	(5)	8	93
2-Methyl-3-pentanone	(6)	18	81
1-Cyclohexylethanone	(7)	16	100
2-Methyl-1-phenyl-1-propanone	(8)	240	100
Nonanal	(9)	5	100

[a]A 4:2:3:1 ratio of NaH:$ZnCl_2$:TMSCl:Substrate was used. [b]See Fig. 1. [c]Yields refer to isolated products. [d]A 1:1 mixture of *cis/trans* isomers.

Discussion

In all investigation, where the influence of several potentially important factors on the result is not known with certainty, it is essential to use an unprejudiced approach. This makes it mandatory to use a multivariate experimental design to allow *all* factors to be considered *simultaneously*. In these cases factorial designs and fractional factorial designs[8] are often useful. Their applications to organic synthesis have been demonstrated in several papers from this laboratory.[9] However, such methods are not widely used in the community of synthetic organic chemists. We wish to point out some advantages of multivariate designs (e.g. factorials, fractional factorials) compared with traditional 'one factor at a time' experiments.

By a factorial design it is possible to determine the main effects of all factors as well as their interaction effects. In contrast, a traditional approach cannot detect any interaction effects. By running fractional factorial experiments it is possible to determine the main effects of all factors in a limited number of runs. Statistical designs are therefore efficient. In a highly fractionated factorial design, main effects and higher interaction effects are confounded. It is, however, easy to resolve any ambiguities either by running a completing fractional design or by a more detailed study (e.g. complete factorial design) with the factors that turned out to be significant in the screening experiments. This latter strategy was followed in this study.

By this we have shown that it is possible to influence the stereochemistry of the reduction of ketones (although to a small extent) by varying the composition of the complex reducing agent. A more important observation was that the rate of reduction is very sensitive to the composition of the reagent. This observation led to an efficient reagent combination from which the alkoxide was excluded. This was an unexpected and *new* result, since Caubere *et al.* have made control experiments in many of their studies. In the majority of cases they found alkoxide to be an essential constituent for the complex reagent to be of any practical use. It should be mentioned that the results of the multivariate study cannot be interpreted in mechanistic terms directly, but any theory about the mechanism of the reaction must, of course, account for the results obtained.

It can be argued that alkoxide is formed during the course of the reduction. However, if this is the crucial factor that makes our modified reagents work, it implies that the reaction is autocatalysed. This, in turn, would imply that the rate could be slow at the beginning of the reaction, when the alkoxide concentration is low, but would increase as the alkoxide concentration becomes higher. This effect has not been observed. In the very beginning of some of the reactions a slightly higher rate was observed (Fig. 1), but this is most likely interpreted as an effect of the temperature increase which occurs during the first minutes after substrate introduction. In most of the cases we have studied, the rate is highest at the beginning of the reaction and decreases as the reaction proceeds, just

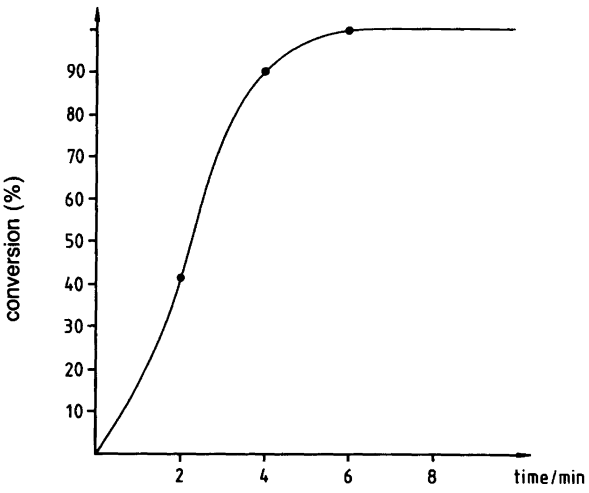


Fig. 1. Approximate rate profile for carbonyl compound **1**.

as expected from lower concentrations of reactants (Fig. 2).

Another difference between Caubere's method and ours is the reagent preparation. They used a more tedious procedure which involves prolonged heating of sodium hydride, zinc chloride and an alkoxide prior to introduction of the substrate. We have shown that this is not necessary to obtain a reactive reagent. Mixing of the constituents of the reagent in tetrahydrofuran at room temperature is sufficient.

Conclusions

Variation of the relative proportions of the constituent ratios of ZnCRASi has a moderate effect on the stereoselectivity of the reduction of 2-methylcyclohexanone. In the special case where alkoxide is completely excluded from the reagent, the reactivity of the reagent is increased. Caubere *et al.* have found that reagents without alkoxide show poor reducing ability. However, in their studies of reagents without alkoxide, they did not include TMSCl in the reaction mixtures. It is therefore concluded that the reactivity of our reagent combination is due to the presence of TMSCl.

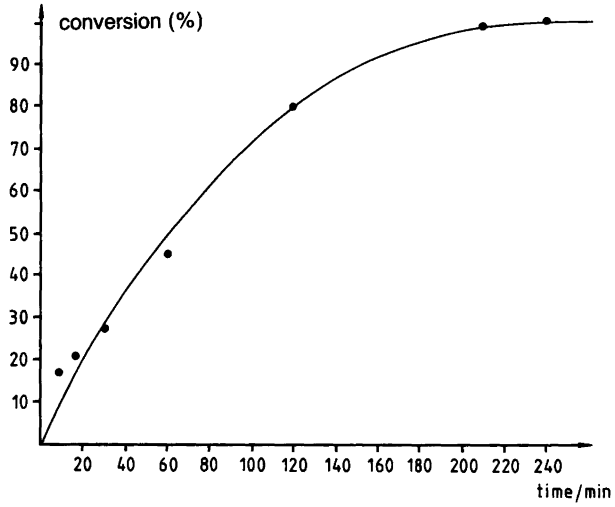


Fig. 2. Approximate rate profile for carbonyl compound **2**.

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Experimental

General. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 80 or a Bruker AC 250 instrument in $CDCl_3$, solution with Me_4Si as an internal shift standard. Mass spectra were recorded using an HP GC/MSD 5830/5970 system. GC analyses were carried out on a Carlo Erba Fractovap 4160 equipped with an FID or on a Carlo Erba Megaseries 5300-HT equipped with an FID. A 15 m Supelcowax 10 0.54 mm or a 15 m SPB-35 0.54 mm capillary column was used. Peak areas were calculated with a Milton Roy CI-10 integrator. All spectra of products were as expected and in accordance with published spectra.

Chemicals and solvent. The chemicals were purchased from Aldrich or Janssen. Liquids were stored over molecular sieves (4A) but otherwise used as received except for TMSCl and tetrahydrofuran (THF). Solids were stored in a desiccator over phosphorus pentaoxide. THF used in the stereochemical study were distilled from sodium–potassium alloy with benzophenone as an indicator. In the preparative experiments, THF stored over molecular sieves (4A) was used as the solvent. TMSCl was distilled under argon from calcium hydride.

Design experiments. The levels of the variables are given in Table 1. The calculated amount, x_1, of sodium hydride (60% dispersion in oil), taking into account one or two extra equivalents for alkoxide formation, was weighed into an oven-dried 100 ml Erlenmeyer flask containing a magnetic stirring bar. The contents of the flask were washed several times with pentane and decanted. The last drops of pentane were evaporated by flushing the flask with nitrogen. The flask was then charged with 20 ml of THF and the contents were stirred. The calculated amount of zinc chloride, x_3, was weighed into a hot test tube and introduced as rapidly as possible into the stirred solution. The calculated amount of *tert*-amyl alcohol, x_2, was weighed into a dry test tube and diluted with 10 ml of THF. This solution was introduced carefully (hydrogen evolution) into the reagent solution. The temperature, x_5, was adjusted and the mixture was stirred for two hours. The calculated amount of TMSCl, x_4, was weighed in a dry glass syringe and was diluted with 10 ml of THF which were drawn into the

syringe. In the cases when a refluxing reagent solution was used, the temperature was lowered before the introduction of the TMSCl solution. The temperature was then readjusted to the high level and stirred for another 15 min prior to the introduction of the substrate.

2-Methylcyclohexanone (1.122 g, 10 mmol) and an accurately weighed amount (ca. 1 g) of nonane (internal standard) were dissolved in 10 ml of THF and introduced as rapidly as possible into the reagent mixture.

Sampling. Aliquots (0.1 ml) were withdrawn at regular intervals and quenched with a two-fold amount of aqueous 2 M HCl. The sample was extracted with pentane and the organic layer was analysed by capillary GLC.

Preparative experiments. Sodium hydride, 40 mmol, was weighed into a dry Erlenmeyer flask and treated as in the design experiments. After dilution with 30 ml of THF, zinc chloride (20 mmol) was immediately added. TMSCl (30 mmol) dissolved in 10 ml of THF was added from a syringe to the reaction mixture. The reaction mixture was cooled to room temperature whereupon 10 mmol of the carbonyl compound (**1–9**) dissolved in 10 ml of THF were added as rapidly as possible to the reaction mixture. The reaction was monitored by GLC. When the reaction was complete (Table 5) the mixture was quenched with 30 ml of 2 M aqueous HCl. The product alcohol could be partially trapped as a silyl ether and to facilitate the hydrolysis to the desired product, a few milliliters of methanol were also added to the reaction mixture. After being stirred for 15 min the mixture was extracted twice with light petroleum (b.p. 40–65 °C). The combined extracts were washed with 5 % aqueous sodium hydrogen carbonate and dried over sodium sulfate. After removal of the drying agent and evaporation of the solvent, the product was weighed and analysed with capillary GC. The purity of the products was > 97 % with the exception of the alcohol from 2-methyl-1-phenyl-1-propanone (**8**) which was 94 % pure.

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