

Dedicated to Prof. Antonius Kettrup on the occasion of his 60th birthday

REDUCTION OF SOLID BENZOPHENONES WITH SODIUM BOROHYDRIDE

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Abstract

The solvent-free reduction of benzophenone and five substituted benzophenones with sodium borohydride to the corresponding alcohols was studied by thermal analysis, X-ray powder diffractometry, NMR spectroscopy, and scanning electron microscopy. In most cases, the reaction occurs via liquid eutectic phases that are formed between the benzophenone and the resulting benzohydrol. Nevertheless, this reaction can be carried out without the need for a solvent, leading to pure alcohol without side products. In some cases, heating may be necessary to achieve a reasonably short reaction time. In conclusion, this reaction type appears to be feasible as a preparative organic reaction that avoids a solvent.

Keywords: benzophenone, reaction kinetics, reduction reactions, solid-state reactions

Introduction

The aim of this study was to contribute to our understanding of thermally initiated organic reactions between two solid components. The general idea was to transpose classical organic synthesis reactions from solution into the solid state, i.e. carrying out reactions like reduction or oxidation between intimately mixed powders.

Such syntheses present promising aspects. If a reaction is carried out between mixed powders, the need for a solvent becomes obsolete. Solvent-free syntheses are seldom applied in organic chemistry, however, the possibility to avoid a solvent that may be toxic, flammable or explosive appears desirable in terms of environmental protection, safety, and, last but not least, cost cutting [1]. Safety and health hazards and cost (purchase and, increasingly today, disposal!) associated

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with most organic solvents are high. The fact that the reaction products of molecular solid-state reactions are often different and smaller in number as compared to the corresponding reaction in solution could be another advantage [2-4], provided that the reaction takes place within acceptable time.

To explore the general applicability of such reactions, we took the pioneering work of Toda *et al.* as starting point. They reported many cases of organic solid-solid reactions that appear of high practical value ([5] for an overview). Reaction times in the order of hours or days were found, frequently with high selectivity and yield. However, the reactions were studied from a preparative point of view, not from a mechanistic point of view. It was not the objective of Toda *et al.* to study the underlying solid-state chemical basis of these reactions. Similar reactions have also been reported by other researchers, e.g. the reaction between *p*-substituted anilines and *p*-benzoquinone [6], intermolecular Michael-type additions [7], and bromination of phenols by N-bromosuccinimide [8].

We have reported earlier about first studies about the reduction reaction of solid benzophenones with sodium borohydride [9] that was discovered by Toda in 1989 [10]. Here we want to complete the study of this reaction type.

Experimental

Experiments with differential scanning calorimetry (DSC) were carried out with a Mettler DSC 27 HP heat-flux calorimeter at ambient pressure. This was calibrated beforehand according to standard recommendations [11-13]. As sample holders we used sealed aluminum crucibles. Empty aluminum crucibles served as reference. The sample mass was between 5 and 10 mg.

For X-ray powder diffractometry, we used a Philips PW 1050/25 diffractometer (Nickel-filter; proportional detector; $\text{CuK}\alpha$ -radiation; $\lambda=154.178$ pm). Intensities were measured as peak integrals. $^1\text{H-NMR}$ was carried out with a Bruker WP-80 MHz instrument and a Varian Gemini 200 MHz instrument. For $^{13}\text{C-NMR}$ spectroscopy the Varian Gemini 200 instrument was used with 50.31 MHz. Scanning electron microscopy was performed with a Philips XL-20 instrument operating at 25 kV with gold-sputtered samples.

Benzophenone (Merck), 4-bromo-benzophenone (Aldrich), 3,4-dichlorobenzophenone (Aldrich), 4,4'-dichloro-benzophenone (Aldrich), 4-methoxy-benzophenone (Aldrich) and 4,4'-dimethoxy-benzophenone (EGA) were all recrystallized from 2-propanol and thoroughly dried in vacuum. The purity was determined calorimetrically by analysis of the melting peak [14]. It exceeded 99.7 mol% in all cases. The purity was also checked in advance by infrared (KBr) and $^1\text{H-NMR}$ (acetone- d_6) spectroscopy. Benzophenone was in its stable modification ($F.p.=49^\circ\text{C}$). Sodium borohydride was purchased from Merck (content >96 %) and used as delivered. It did not contain water, as verified by thermogravimetry and DSC.

Before the reaction, sodium borohydride and the benzophenone were thoroughly ground together in an agate mortar. Approximately 200 mg of the mixture were then pressed into pellets (diameter 12.4 mm, thickness 1.5 mm). The X-ray powder diffractograms of such pellets showed no differences to powder samples, therefore we can exclude pressure-induced phase transformations.

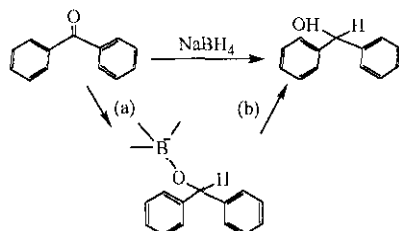
For determination of the reaction extent α by NMR, a sample aliquot was hydrolyzed in aqueous 2-molar HCl. The organic components were extracted with diethyl ether that was then dried with sodium sulphate. The ether was distilled off, and the remaining benzophenone/benzohydrol mixture was dissolved in acetone- d_6 for ^1H -NMR analysis. Quantitative determination of α was performed by comparing the intensity of the benzohydrol methine proton with the intensity of the aromatic protons.

The molar ratio of benzophenone to sodium borohydride was 1:1, unless otherwise noted. To enhance the reaction and to standardize the reaction conditions, 1 mol H_2O per mol NaBH_4 was added before the reaction (formal composition: "benzophenone· NaBH_4 · H_2O ").

Results and discussion

In order to assess the full potential of such a promising synthetic method that avoids a solvent, it is necessary to study the reaction rate as a function of external and internal parameters. Consequently, we have applied different analytic techniques to the reacting mixture. The reaction was followed *ex situ* by ^1H - and ^{13}C -NMR, infrared spectroscopy (IR), X-ray powder diffractometry and scanning electron microscopy.

In Ref. [10], Toda described the reaction as a simple reduction from ketone to alcohol and did not consider mechanistic aspects. Only educt and product phases were identified. A closer inspection of the reaction reveals that water is necessary to lead it to completion:



Possible reaction intermediates are boric acid esters $\text{Na}^+[\text{B}(\text{OR})_n\text{H}_{4-n}]^-$ ($n=1-4$). The inorganic reaction product after hydrolysis must be sodium orthoborate $\text{Na}^+\text{B}(\text{OH})_4^-$ or a similar compound, possibly a condensed borate. Obviously, the reaction is more complex than it appears at first.

We have found earlier that the reaction between benzophenone and sodium borohydride occurs via a liquid eutectic phase containing benzophenone and

benzohydrol that forms after some benzophenone has been reduced. After this initial step, the reaction mixture liquefies until the solubility of benzohydrol is exceeded. At this point, benzohydrol crystallizes out of the melt. This is clearly visible in *ex situ* X-ray powder diffractometric experiments [9].

Furthermore, water was shown to be essential for the reaction. An increasing water content enhances the reaction [9]. Since the preceding study, we have been able to prepare and store a reaction mixture under complete water exclusion. A sample of a thoroughly dried benzophenone/ NaBH_4 mixture was placed into a dry Schlenk tube and kept there for 50 days at room temperature. After that time, the Schlenk tube was opened and the sample was immediately analyzed with IR and $^1\text{H-NMR}$. It showed no detectable conversion into benzohydrol.

This observation demonstrates that the presence of traces of water is essential for the reaction. For the first reaction step to a boric acid ester (reaction (a) in Eq. (1)), no water is necessary. For the subsequent hydrolysis to benzohydrol (reaction (b) in Eq. (1)), it is needed in stoichiometric amounts. The absence of reactivity under complete water exclusion points to a decisive influence of water on reaction (a). The mechanistic reason is not known, but possibly water dissolves some NaBH_4 and thus initiates the reaction. Also, water may induce lattice defects and thereby increase the mobility of the reactants [15].

The reactivity of a mixture of benzophenone and $\text{NaBH}_4 \cdot \text{H}_2\text{O}$ in the molar ratio of 0.275:1 was followed to see whether all hydrogen atoms are equally reactive (in principle, each NaBH_4 unit can reduce four benzophenone molecules). The results are shown in Fig. 1. Interestingly, steps show up at $\alpha=0.55$ and 0.75. This observation suggests a different reactivity of the hydrogen atoms, with the first two being very reactive and the fourth almost unreactive. Consequently, intermediate boranate phases must have formed.

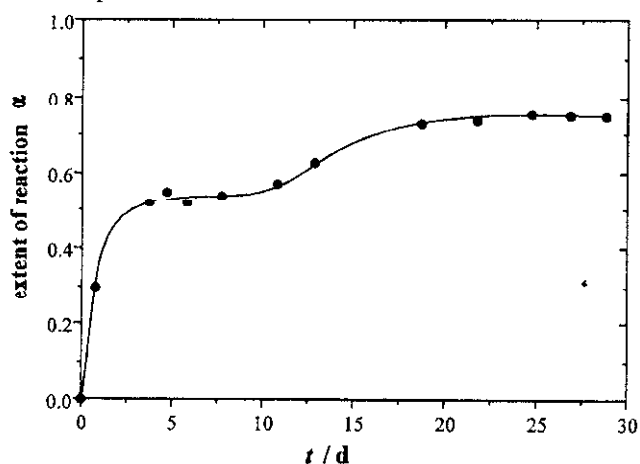


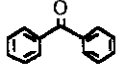
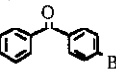
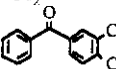
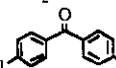
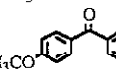
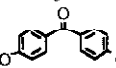
Fig. 1 Reaction extent as determined by $^1\text{H-NMR}$ for the reaction of benzophenone with NaBH_4 ($n:n=1:0.275$) at room temperature. The reduction occurs in several steps. The line represents an arbitrary fit function to the data

The reduction of five other substituted benzophenones was studied. They are all higher melting than benzophenone. The corresponding alcohols were prepared by conventional reduction with NaBH₄ in isopropanol. Three out of the six benzohydrols did not crystallize, although two of them were reported as crystalline [16]. The results of our thermoanalytic investigations are summarized in Table 1. Obviously, this reduction reaction is not equally feasible for all kinds of benzophenones.

In the cases where the pure corresponding alcohol could be obtained, the phase diagram was determined by DSC. It was found that benzophenone/benzohydrol and 4-bromo-benzophenone/4-bromo-benzohydrol form simple eutectic

Table 1 Characteristic data of the investigated benzophenones and benzohydrols.

Thermodynamic data and purity were determined by DSC unless otherwise indicated

Substituents on benzophenone rings		$T_{fus}/^{\circ}C$	$\Delta_{fus}H/kJ\ mol^{-1}$	Purity/mol%	$T_{eut}/^{\circ}C$	$x_{eut}(x_{alcohol})$	Reactivity at 25 ^o C
-H	ketone	49.1	19.4	99.8	24.4	0.38 ^b	$\alpha=1$ after 2 days
	alcohol	67.1	23.1	99.8			
4-Br	ketone	80.4	24.4	99.9	31.3	0.57 ^b	$\alpha=1$ after 2 days
	alcohol	63.2	20.1	99.8			
3,4-Cl ₂	ketone	101.5	30.2	99.9	<25 ^d	?	$\alpha=1$ after 9 days
	alcohol	-	-	-			
4,4'-Cl ₂	ketone	146.1	30.9	99.9	$\approx 75^c$	>0.65 ^c	$\alpha=0.3$ after 80 days
	alcohol	92.9	26.5	99.8			
4-CH ₃ O	ketone	60.9	21.7	99.9	<50	?	no reaction within 2 days
	alcohol	65-68 ^a	-	-			
4,4'-CH ₃ O	ketone	143.0	33.5	99.9	?	?	no reaction within 120 days
	alcohol	70-72 ^a	-	-			

^a Taken from Ref. [16]

^b Simple eutectic phase diagram. Similar values for benzophenone/benzohydrol were reported in Ref. [28]

^c The phase diagram consists of a number of phases, both stable and metastable. It could not be completely determined. Eutectic points were found on the alcohol-rich side of the phase diagram with melting temperatures of 75 and 80^oC

^d This value was derived from the reactivity studies (see text)

phase diagrams with an eutectic temperature near room temperature (Table 1). It is therefore assumed that the reaction proceeds via a liquid stage. Liquefaction was also observed for 3,4-dichloro-benzophenone, therefore the eutectic temperature must be near room temperature as well.

The lowest melting point in the case of 4,4'-dichloro-benzophenone/4,4'-dichlorobenzohydrol was 75°C. This could explain the low reactivity (Table 1). This phase diagram is of more complex nature. The phase diagrams for the two methoxy-substituted compounds were not determined.

Interestingly, the solid-state reduction of 4-bromo-benzophenone to 4-bromo-benzohydrol led to a different polymorphic phase compared to that obtained by conventional reduction in solution. ¹H-NMR and IR proved the chemical identity, however, the XRD pattern was different, and the melting temperature was determined to 53.9°C instead of 63.2°C (Table 1). As the melting point is lower, the new phase must be metastable with respect to the phase obtained from solution [17–19].

The effect of storage temperature was studied for 4-methoxy-benzophenone and 4,4'-dichloro-benzophenone. In order to avoid any artifacts, the following procedure was adopted: benzophenone and NaBH₄·H₂O were thoroughly mixed in an agate mortar. A number of pellets was pressed, and each pellet was stored in a separate closed Schlenk tube at the chosen reaction temperature. At selected times, one Schlenk tube was cooled to room temperature and the pellet was analyzed by X-ray powder diffractometry, IR spectroscopy and ¹H- and ¹³C-NMR in solution. If no immediate work-up was possible, the sample was stored at -20°C. The pellets were weighed before and after the annealing to ensure that no water had escaped the Schlenk tube. The sample mass was usually constant within ±0.5%.

The reaction rate was determined for 4,4'-dichloro-benzophenone at 25, 40, 50, 60, 70 and 80°C. The corresponding α/t -values are shown in Fig. 2. The reaction rate increases considerably with rising temperature. Although no simple mechanism seems to be involved (and is not expected for such a complicated system), a rough measure of the reaction rate is provided by the time to reach the half-conversion $\alpha=0.5$. This is plotted in Fig. 3 against the reaction temperature. The data points lie on a straight line as first approximation; however, a kink might be suspected around $T\approx 65^\circ\text{C}$. This would agree well with the observation from above that the lowest eutectic temperature in this system is around 75°C. Below this temperature, the reaction rate is controlled by diffusion in the solid state, above the temperature a liquid eutectic phase forms. Once this temperature is reached, the activation energy necessary for diffusion decreases, and the change in reaction rate with temperature becomes smaller. However, as many simplifications are involved in Fig. 3, one should take this conclusion with care.

With none of the applied methods an intermediate could be detected. All samples were crystalline in X-ray powder diffractometry. However, as the samples were reacted at higher temperature and analyzed after cooling to room tempera-

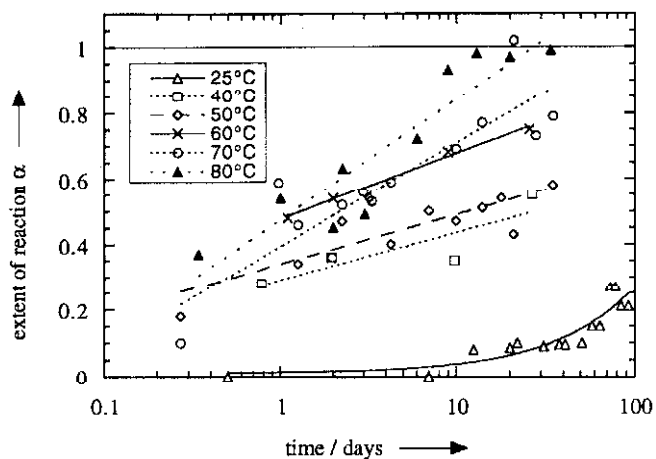


Fig. 2 Reaction extent as determined by $^1\text{H-NMR}$ for the reaction of 4,4'-dichloro-benzophenone with NaBH_4 ($n:n=1:1$) at different temperatures. The lines represent arbitrary fit functions to the data

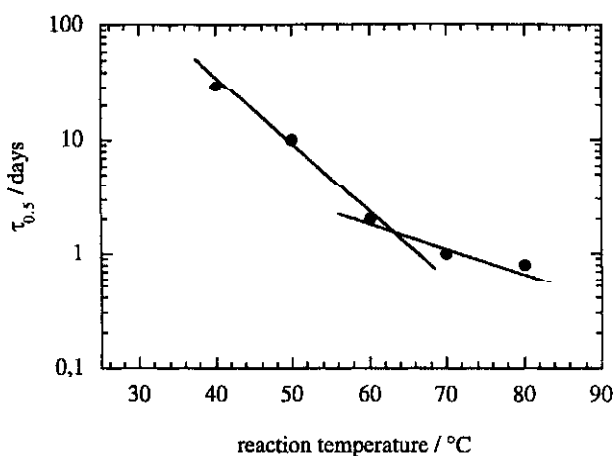


Fig. 3 Time needed to achieve $\alpha=0.5$ vs. the reaction temperature for the reaction between 4,4'-dichloro-benzophenone and NaBH_4 . Data taken from Fig. 2

ture, we cannot rule out liquefaction and subsequent crystallization upon cooling.

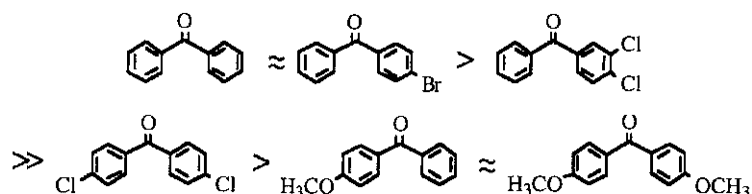
Isothermal DSC experiments of 1:1:1 mixtures of 4,4'-dichloro-benzophenone/ $\text{NaBH}_4/\text{H}_2\text{O}$ were carried out between 70 and 140°C. At 70°C, no reaction occurred, whereas at the higher temperatures an exothermic peak appeared. Its enthalpy was almost constant ($-23.5 \pm 1.3 \text{ kJ mol}^{-1}$) and is ascribed to the reduction reaction. The reaction extent was determined by $^1\text{H-NMR}$ after the DSC experiments and found to be between $\alpha=0.71$ and 0.86. Note that the determination

of α is very inaccurate with such small sample quantities, however, the main part of the sample has reacted. Reaction times were between ca. 850 min at 80°C and ca. 100 min at 140°C. In all cases, a sharp exothermic peak within the first 20 min was followed by a broad exothermic peak.

We can ascribe this exothermic enthalpy to the reduction reaction. The fact that it is smaller than comparable values (e.g. reduction of cyclohexanone with NaBH_4 in isopropanol: $-52.3 \text{ kJ (mol ketone)}^{-1}$ [20]) can be explained by incomplete conversion or a possibly liquid benzohydrol phase. Additionally, a decrease of ring strain from cyclohexanone to cyclohexanol may increase the negative value of the reaction enthalpy in that case. In general, the comparison of enthalpies for the same reaction carried out in the liquid and in the solid state is problematic because (large) lattice and solvation energies contribute to the (small) reaction enthalpy.

Samples of 4-methoxy-benzophenone did not react at room temperature. An *ex-situ* experiment at 50°C (carried out as above) showed almost complete amorphization after 18 h, followed by crystallization of 4-methoxy-benzohydrol ($\alpha=1$ after 4 days). Therefore we assume that the eutectic temperature in this system is between 25 and 50°C.

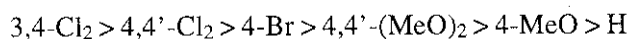
Summarizing these results, the following order of reactivity can be formulated:



A number of effects are determining the reactivity of substituted benzophenones. The main influence factors should be

- the melting temperature of the benzophenone (influences the mobility of molecules in the crystal), and likewise
- the melting temperature of the benzohydrol
- the melting temperature of eutectic mixture, as liquid phases enhance the reaction due to higher mobility of the reacting species [21]
- in cases where a true solid state reaction occurs, the crystal structure should determine the reactivity
- electronic effects of the substituents on the aromatic ring could influence the reactivity in the same way as they do for the same reaction in solution.

Bowden and Hardy studied the kinetics of the reduction of substituted acetophenones with NaBH_4 in isopropanol at 30°C [22]. If one transposes these results to the benzophenone system, the following order of reactivity is obtained:



This differs considerably from the order found for this solvent-free reaction, stressing the inherent difference between reactions in solution and between solids [22].

These are "internal" parameters beyond our control. External parameters of interest are

- the reaction temperature
- the water content
- the contact area between the reactants

It is not possible to separate all these effects with the available data material. As reactions involving solids are in general of high complexity [23], this is not unexpected. However, in this case the occurrence of intermediate liquid phases appears to be crucial for the reactivity.

The kinetic results presented above were all derived from NMR spectroscopy and X-ray powder diffractometry. To understand the microscopic changes that determine the solid-state reactivity, it is indispensable to "look" on the sample with more specific methods, especially with microscopy. The study of morphology changes and phase boundaries during solid-state reactions can often provide deeper insight into the mechanism [23–27].

Some of the samples of 4,4'-dichloro-benzophenone and NaBH₄ that were reacted at higher temperature were studied by scanning electron microscopy. The pellets were sputtered with gold and analyzed immediately thereafter. Figures 4 and 5 show some representative pictures. A freshly prepared pellet of 4,4'-dichloro-benzophenone and NaBH₄ has a more or less smooth surface. After 35 days at 70°C, the surface has adopted a distinct microstructure. In particular, it has become very rough, and piles of crystals can be seen. Needles and "balls" are formed. The reaction extent was 79% for this pellet.

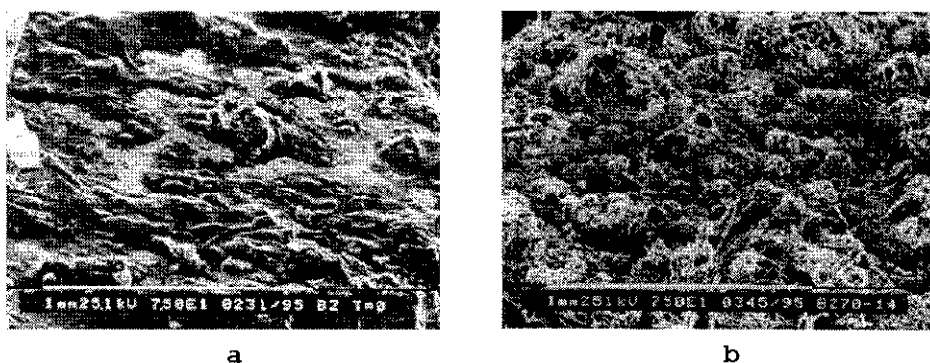


Fig. 4 Scanning electron micrographs taken during the reaction of 4,4'-dichloro-benzophenone with NaBH₄. a) surface of a pellet before the reaction (75×); b) surface of a pellet after 35 days at 70°C with $\alpha=79\%$ (75×)

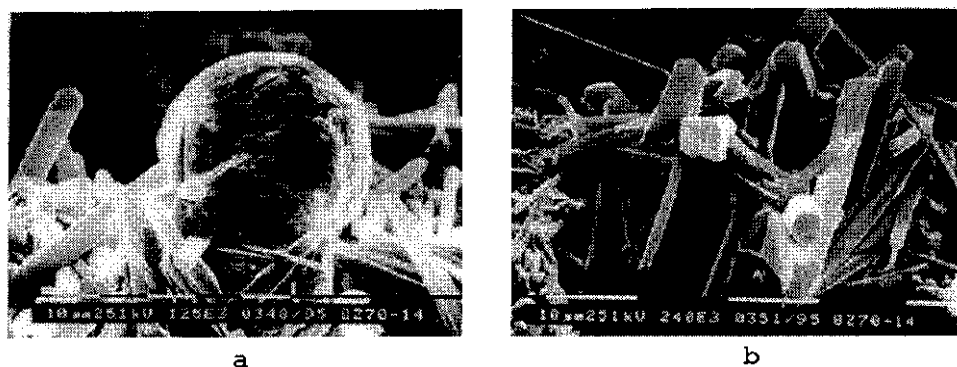


Fig. 5 Scanning electron micrographs taken during the reaction of 4,4'-dichloro-benzophenone with NaBH_4 . a) a sodium containing aggregate (1250 \times); b) the product 4,4'-dichloro-benzohydrol (2400 \times)

By energy-dispersive X-ray diffraction analysis (EDX) it was found that the "balls" consist of a sodium-rich phase with no chlorine present whereas the "needles" consist of a chlorine-rich phase with no sodium present. This shows that the needles are the product phase, 4,4'-dichloro-benzohydrol, that recrystallized after the conversion. The needles are well crystallized with sharp edges and lengths of up to 50 μm . Sodium borohydride and its oxidation product(s) form the spherical aggregates. In X-ray powder diffractometry, no peaks of an inorganic reaction product could be detected, therefore this sodium borate phase must be amorphous.

The overall morphology with sodium borate "balls" in the midst of 4,4'-dichloro-benzohydrol points to extensive diffusion and recrystallization phenomena during the reaction.

If the reduction of benzophenones with sodium borohydride occurred as a solid-state reaction in a topochemical way, the crystal structures of educt and product phases would be of decisive influence. As shown in the previous sections, the reduction of benzophenones with sodium borohydride does not occur in the solid state but via liquid intermediate phases. Therefore the crystal structure has practically no influence on the reactivity, besides, possibly, in the very first stages of the reaction. The only case where a reaction at least partially occurs in the solid state is 4,4'-dichloro-benzophenone.

Conclusions

A number of analytical techniques was applied to study the reaction of six solid benzophenones with solid sodium borohydride NaBH_4 . The results confirm the occurrence of liquid eutectic phases during the reaction, indicating that the reaction does not completely take place in the solid state. Increasing the tempera-

ture strongly accelerates the reaction, probably again due to formation of low-melting eutectic mixtures with a melting point above room temperature.

The water content in a reaction mixture is of decisive influence. Under strict water exclusion, the reaction does not occur whereas the presence of water strongly enhances the reaction. There are indications that not all hydrogen atoms are equally reactive, i.e., intermediate boranate phases occur.

The reduction reaction is possible for five out of six examined benzophenones. In the sixth case, a reaction could probably also be induced by an increase in temperature. No side-products were detected with the available methods, and the reactions lead to full conversion. This could point to a general applicability of such a synthesis without solvent. The fact that the reaction time is long compared to a reduction in solution may be overcome by a higher reaction temperature.

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We thank Prof. A. Reller for generous support, Prof. H. Lechert for the permission to use the scanning electron microscope and A. Krummland for experimental assistance. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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