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Organic solid–solid reactions: exploration of the synthetic potential[☆,1]

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Abstract

The reduction reaction of a number of benzophenones with sodium borohydride in the solid state was studied. This type of organic solid-state reaction, avoiding a solvent, can be useful in chemical synthesis. The reaction was followed by in situ X-ray powder diffractometry and by ^{1}H NMR spectroscopy on subsequently taken aliquots. We found a strong dependence of the reaction rate on the water content of the mixture and on the type of benzophenone.

Keywords: Benzophenone; Organic solid state chemistry; Reduction reactions; Solid state reactions; X-ray powder diffractometry

1. Introduction

Organic solid–solid reactions may present promising aspects for chemical synthesis. In this reaction type, the reaction is carried out between mixed powders, without the use of a solvent. The desirable possibility of avoiding a solvent that may be toxic, flammable or explosive was pointed out by Seebach in a review article on the future of organic chemistry [1]. Often the products of an organic solid state

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reaction are different from those of the same reaction in solution [2]. This should open new directions for organic synthesis, provided that the reaction takes place in acceptable time.

A number of examples of organic solid–solid reactions have been reported by Toda and coworkers. They studied oxidation reactions [3], reduction reactions [4, 5], coupling reactions [6, 7] and molecular rearrangements [8] (see Ref. [9] for an overview). Reaction times in the order of hours or days were reported, with frequently high selectivity and yield.

For the reduction of ketones with sodium borohydride, $NaBH_4$, Toda et al. reported high reaction yields after a 5-day reaction time of the mixed powders (ketone: $NaBH_4 = 1:10$) in a dry box at room temperature [4]. The mixture was "stirred" once every day. After the reaction time, the mixture was extracted with ether, which was distilled off to obtain the corresponding alcohol. For benzophenone and 4-bromo-benzophenone, they obtained a 100% reaction extent. No attempt was made to study the influence of experimental conditions, or to elucidate the kinetics or mechanism of this solid state reaction.

For a general applicability of such a method of synthesis, it is desirable to learn more about the reaction rate and its dependence on the external or internal parameters, in order to optimize the yield. In this work, we concentrate on the reduction of a group of chemically similar ketones, benzophenones. These were reduced with solid sodium borohydride under carefully defined conditions. The reaction was followed by NMR on sample aliquots and continuously by X-ray powder diffractometry.

2. Experimental

DSC experiments for the determination of the phase diagram benzophenone–benzhydrol were carried out on a Heraeus TA 500 heat-flux calorimeter that had been calibrated according to Ref. [10–12]. All other DSC experiments were made on a Mettler DSC 27 HP high-pressure heat-flux calorimeter, operated at ambient pressure. This calorimeter was calibrated by the fusion temperatures of indium, lead and zinc, and by the enthalpy of fusion of indium, according to the manufacturer's recommendation. In both instruments, we used sealed aluminium capsules and empty reference capsules.

For X-ray powder diffractometry (XRD), we used a Siemens D5000 diffractometer with secondary monochromator and scintillation detector, and a Philips PW1050/25 diffractometer with a nickel filter and proportional detector. Both were operated with Cu Kα radiation ($\lambda = 154.178$ pm). Intensities were measured as peak integrals using asymmetric Pearson VII fit functions.

We used the following benzophenones for the solid-state reactions: benzophenone (Merck), 4-bromo-benzophenone (Aldrich), 3,4-dichloro-benzophenone (Aldrich), 4,4′-dichloro-benzophenone (Aldrich) and 4,4′-dimethoxy-benzophenone (EGA). They were recrystallized from 2-propanol and thoroughly dried in vacuum. The purity was determined calorimetrically [13]. It exceeded 99.7 mol% in all cases. Benzophenone was in its stable polymorphic modification, melting at 49°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 in an agate mortar. Approximately 200 mg of the mixture were then pressed into tablets (diameter 12.4 mm, thickness 1.5 mm; IR press, 30s at 25 bar). No change in the X-ray diffractogram was observed for tablets in comparison with powdered samples, therefore pressure-induced phase transitions can be excluded. During the reaction, the tablets were sealed with mylar foil and stored in a dry box to prevent the access of water.

For determination of the reaction extent by NMR, a sample aliquot was hydrolysed in aqueous 2 M HCl. The organic components were extracted with diethyl ether and then dried with sodium sulphate. The ether was distilled off, and the remaining benzophenone/benzhydrol mixture was dissolved in acetone-d_6 for NMR analysis.

^{1}H NMR was carried out with a Bruker WP-80 80 MHz instrument. By comparing the intensity of the benzhydrol methine proton (benzylic proton) with the intensity of the aromatic protons, it is possible to calculate the ratio of benzhydrol to benzophenone, and the reaction extent. By measuring NMR spectra of defined mixtures of benzhydrol and benzophenone, we ensured that there is a linear relationship between peak intensity ratio and the molar fraction.

The molar ratio of benzophenone to sodium borohydride was 1:1 in all experiments. All reactions were carried out at room temperature.

3. Results and discussion

Toda described the reaction as a simple reduction from ketone to alcohol and did not consider any mechanistic aspects. A closer inspection leads to the following reaction equations

$$(C_6H_5)_2C{=}O + BH_4^-Na^+ \longrightarrow (C_6H_5)_2CH{-}O{-}BH_3^-Na^+ \quad (1)$$

$$(C_6H_5)_2CH{-}O{-}BH_3^-Na^+ + H_2O \longrightarrow (C_6H_5)_2CH{-}O{-}H + HO{-}BH_3^-Na^+ \quad (2)$$

Other reaction products may be higher boric acid esters $Na^+B(OR)_nH_{4-n}^-$ ($n = 2$–4) and sodium orthoborate $Na^+B(OH)_4^-$. Therefore, the reaction is more complex than assumed at first, with a number of possible intermediates. Clearly, water is necessary to hydrolyse the boric acid ester to give the desired benzhydrol.

Results of the reduction of benzophenone with $NaBH_4$ monitored by X-ray powder diffractometry are shown in Fig. 1. The X-ray data show the decrease in intensity of the benzophenone peaks, e.g. $2\Theta = 18.31°$ (021), $2\Theta = 20.25°$ (121), $2\Theta = 22.18°$ (002) [14, 15], up to an X-ray amorphous state. This turned out to be a liquid phase (see below). After some days, benzhydrol begins to crystallize, and diffraction peaks of benzhydrol begin to grow, e.g. $2\Theta = 19.00°$ (400), 23.05° (250) [16]. Sodium borohydride peaks are not present in the angular range shown. They show a decrease during

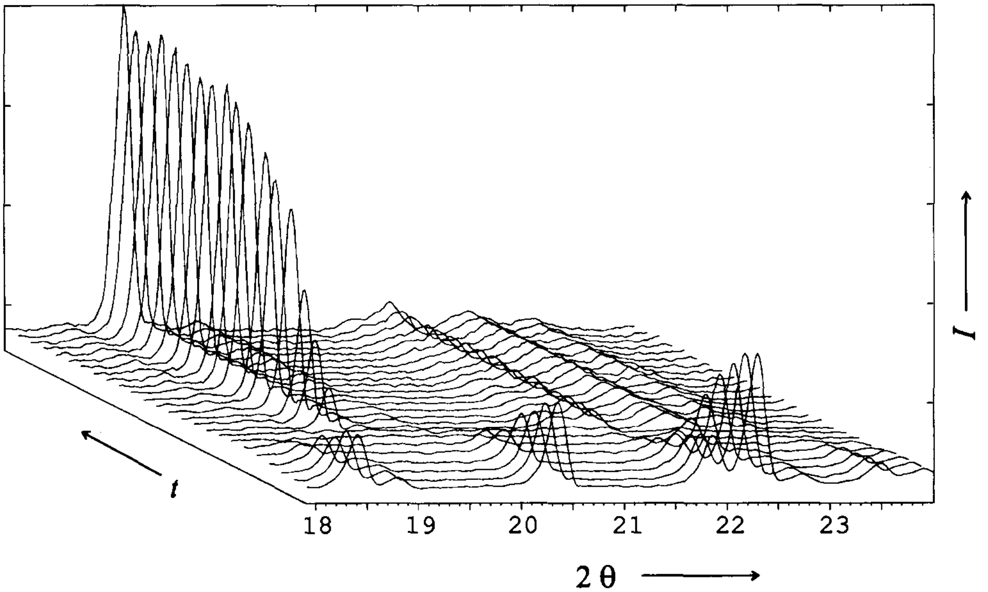

Fig. 1. Three-dimensional representation of X-ray powder diffraction data for the reduction of benzophenone with sodium borohydride at room temperature (n(benzophenone): $n(NaBH_4) = 1:1$). Benzophenone peaks vanish, and following an amorphous phase, benzhydrol peaks begin to grow. Sodium borohydride has no peaks in this angular range. Note that the time period between the scans is not constant. The first 7 scans were recorded during 2 days, then the time intervals were increased. For details of time resolution see Fig. 2.

the reaction, but do not vanish during the amorphous phase. No additional peaks of intermediates could be detected (but note that these must be crystalline to be detectable!).

The quantitative evaluation of this reaction is displayed in Figs. 2 and 3. Selected strong X-ray peak intensities of benzophenone and benzhydrol were normalized to their maximum intensities, respectively. These normalized intensities are proportional to the mass fractions of the corresponding compound in the reaction mixture. Only the fraction of the compound in its solid state contributes to the X-ray scattering; the liquefied fraction does not scatter the X-rays. Accordingly, the normalized intensity is proportional to the mass fraction of the compound in the solid state in the mixture. The change in mass absorption coefficient during the reaction is negligible; therefore no correction is necessary [17].

In addition Fig. 2 contains the reaction extent determined by ^{1}H NMR spectroscopy. Neither the rapid decay of the benzophenone XRD peak nor the slow growth of the benzhydrol XRD peak correspond to the reaction progress measured by NMR. This can be explained as follows. Benzophenone and benzhydrol form a simple eutectic mixture. The eutectic temperature is 24.4(10)°C at $x_{\mathrm{Benzophenone}} \approx 0.62$, as determined by DSC. At room temperature, the mixture is liquid. As soon as some benzhydrol is

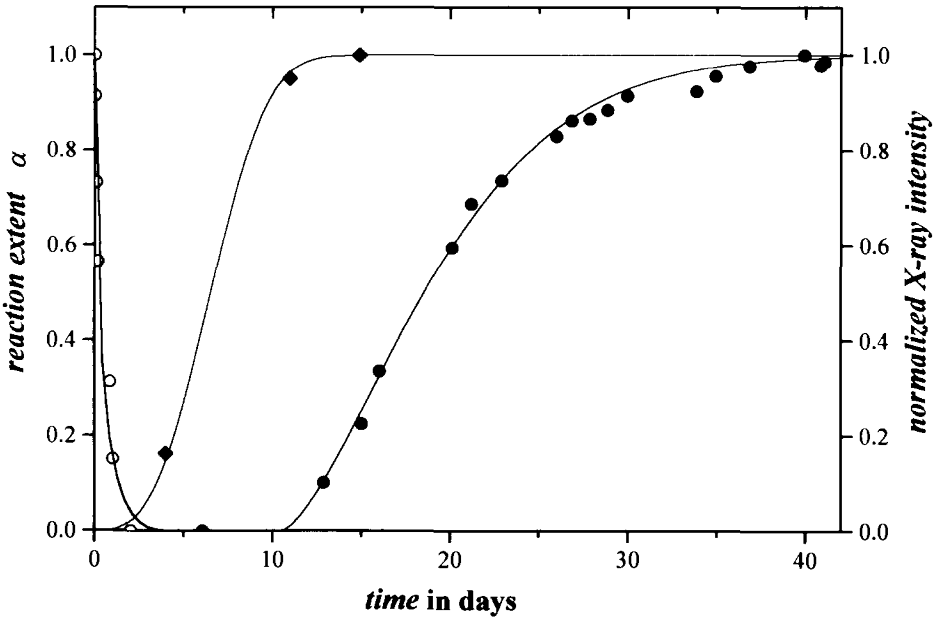

Fig. 2. NMR-spectroscopically-determined reaction extent vs. time for the reduction of benzophenone with sodium borohydride (◆). For comparison, normalized peak intensities from an identical reaction mixture for a benzophenone and a benzhydrol peak are shown: ○, benzophenone (121) peak at 2Θ = 20.25° 2Θ, and ●, benzhydrol (400) peak at 2Θ = 19.00° 2Θ. The benzophenone peaks decrease rapidly during the first 2 days. Clearly visible is the X-ray-amorphous (liquid) period between $t = 2$ days and $t = 12$ days. After 12 days, benzhydrol begins to crystallize. Liquefaction of the mixture occurs on account of the formation of a low-melting eutectic mixture of benzophenone and benzhydrol.

formed, benzophenone forms a eutectic mixture and no longer contributes to the X-ray scattering. This leads to a rapid decay in intensity. During the intermediate reaction state, a completely liquid eutectic mixture is present. In the latter stages of reaction, the solubility of benzhydrol is exceeded, and it begins to crystallize. The "hidden" benzhydrol in the liquid phase is not detectable by X-ray diffractometry. The growth of the diffraction peak is related to the crystallization rate of benzhydrol. The presence of a liquid stage means that we do not have a true solid state reaction, even though educts and products are all solid.

The water necessary to hydrolyse the boric acid ester must be provided by diffusion through the sealing foil. It cannot be decided at this stage whether the kinetics of the reduction reaction or the diffusion of water are rate-determining. Because of the very high hygroscopicity of the boric acid esters, we have not yet been successful in monitoring a reaction under complete water exclusion.

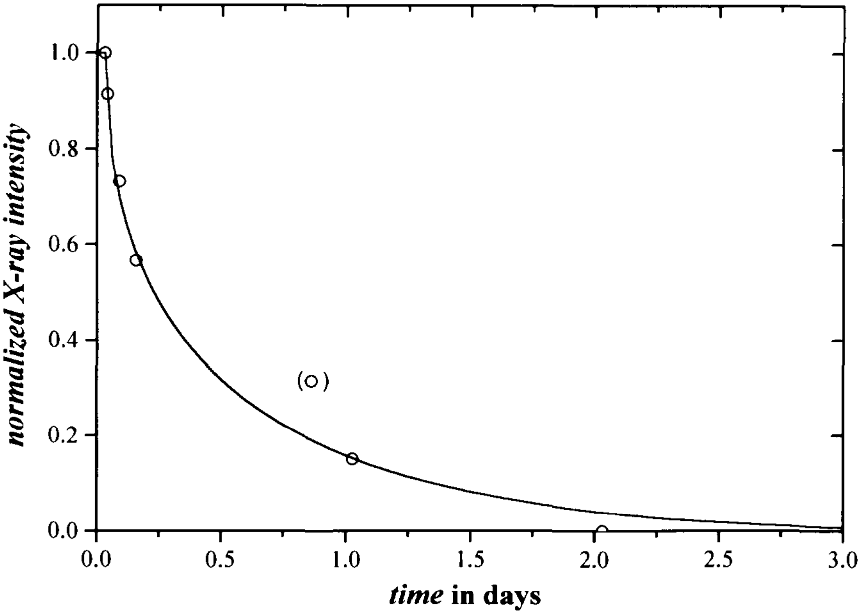

Fig. 3. The decreasing scattering intensity of the benzophenone (121) peak during the first days. Magnified data from Fig. 2.

Obviously, water has a strong influence on the reaction rate. To study this effect, we prepared samples with defined water contents, i.e. water was added to the sodium borohydride before mixing and pressing the sample. This water is bound by sodium borohydride as dihydrate, which we identified by X-ray diffractometry [18]. The dihydrate decomposes a little above room temperature to sodium borohydride and liquid water. The added water leads to the nominal sample composition "$NaBH_4 \cdot H_2O \cdot$benzophenone".

The reaction progress for benzophenone samples with varying water content is shown in Fig. 4. The presence of water increases the reaction rate considerably. This can be understood with Eqs. (1) and (2), which show that water takes part in the reduction reaction sequence. A catalytic effect of water was computed with quantum mechanical methods for the reduction of formaldehyde with $NaBH_4$ in the gas phase [19]. A similar mechanism could be applicable here.

Finally, we studied the reduction of four other benzophenones. They are all higher melting (4-bromo, 80.4°C; 3,4-dichloro, 101.6°C; 4,4′-dichloro, 146.1°C; 4,4′-dimethoxy, 145.1°C) than benzophenone (49.2°C). The melting temperatures of the corresponding alcohols are 67.1°C (benzhydrol), 63.2°C (4-bromo), < 25°C (3,4-dichloro) and 92.9°C (4,4′-dichloro). The 4,4′-dimethoxy-benzhydrol did not crystallize, but is expected to melt above room temperature. All melting temperatures were measured by us with DSC. The phase diagrams of these four benzophenones and the corresponding benzhydrols are not yet known.

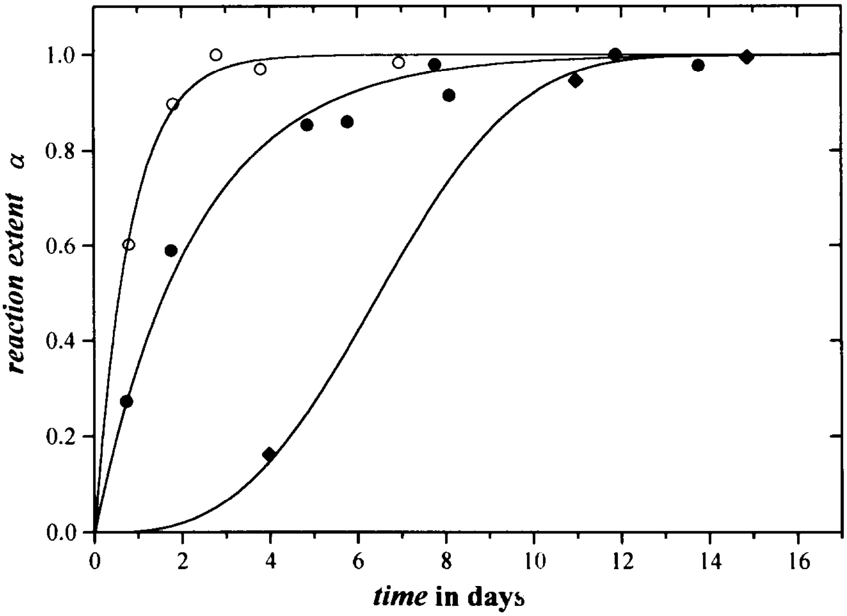

Fig. 4. Reaction extent vs. time for benzophenone samples with different water content, determined by NMR. The presence of water strongly enhances the reaction: ○, nominal sample composition "$NaBH_4 \cdot H_2O$" + benzophenone, stored in air (free access of atmospheric water); ●, nominal sample composition "$NABH_4 \cdot H_2O$" + benzophenone, stored in a dry box; ◆, no water added to the sample, stored in a dry box.

To enhance the reaction, we added 1 mol of H_2O per mol of $NaBH_4$ before the reaction (nominal composition "$NaBH_4 \cdot H_2O$"). The results are shown in Fig. 5. Values for 4,4′-dichloro-benzophenone and 4,4′-dimethoxy-benzophenone are not shown. These compounds need significantly more time than 10 days to react. In fact, for 4,4′-dimethoxy-benzophenone, no reaction was observed even after storing for 3 months.

The following order of reactivity can be formulated

$$\text{Benzophenone} \approx \text{4-Br} > \text{3,4-}Cl_2 \gg \text{4,4'-}Cl_2 > \text{4,4'-}(CH_3O)_2$$

A number of effects determine the reaction rate. For instance, the melting temperature of the benzophenone (influences the mobility of molecules in the crystal), the melting temperature of the eutectic mixture or of the corresponding benzhydrol itself (liquid phases enhance the reaction [20]) and the crystal structure (steric availability of carbonyl groups) should be important. Finally, electronic effects of the substituents on the aromatic ring can influence the reactivity. It is not possible to separate these effects with the available data.

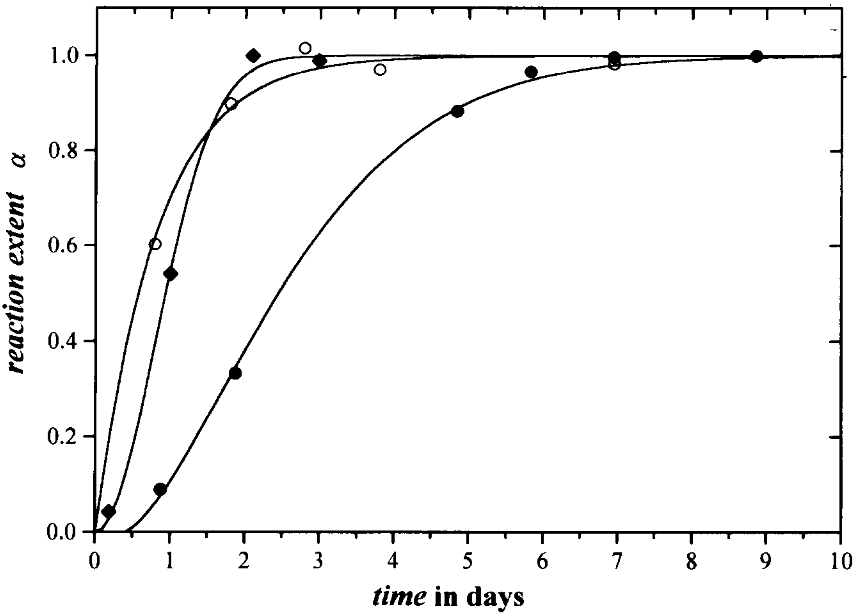

Fig. 5. Reaction extent vs. time for 3 different benzophenones with nominal sample composition "$NaBH_4 \cdot H_2O$" + benzophenone. The reaction extent was determined by NMR: ○, benzophenone; ◆, 4-bromo-benzophenone; ●, 3,4-dichloro-benzophenone.

The reduction of benzophenone and 3,4-dichloro-benzophenone occurs via liquid phases, namely, eutectic mixture and 3,4-dichloro-benzhydrol, respectively. In the three other cases, no liquid phase could be observed.

4. Conclusions

The reduction reactions of five benzophenones with sodium borohydride $NaBH_4$ were studied in the solid state by NMR spectroscopy and X-ray powder diffractometry. In two cases, liquid phases occur during the reaction. The water content in a reaction mixture is of decisive influence. With very dry samples, the reaction needs weeks to complete, even for the most reactive compounds benzophenone and 4-bromo-benzophenone. The presence of water strongly enhances the reaction. It may be suspected that the results of Toda et al. (100% reaction extent in 5 days for benzophenone and 4-bromo-benzophenone) [4] were obtained in the presence of some atmospheric water. The reduction reaction is possible for four out of the five examined benzophenones. 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 using a higher reaction temperature, a parameter we have not yet investigated. Overall, organic solid–solid reactions may eventually supplement the synthetic arsenal of preparative chemists.

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References

[1] D. Seebach, Angew. Chem., 102 (1990) 1363–1409; Angew. Chem. Int. Ed. Engl., 29 (1990) 1320.
[2] J.M. Thomas, Pure Appl. Chem., 51 (1979) 1065–1082.
[3] F. Toda, M. Yagi and K. Kiyoshige, J. Chem. Soc: Chem. Commun., (1988) 958.
[4] F. Toda, K. Kiyoshige and M. Yagi, Angew. Chem., 101 (1989) 329–330; Angew. Chem. Int. Ed. Engl., 28 (1989) 320.
[5] F. Toda and K. Mori, J. Chem. Soc: Chem. Commun., (1989) 1245–1246.
[6] F. Toda, K. Tanaka and S. Iwata, J. Org. Chem., 54 (1989) 3007–3009.
[7] F. Toda and Y. Tokumaru, Chem. Lett., (1990) 987–990.
[8] F. Toda and T. Shigemasa, J. Chem. Soc. Perkin Trans. 1, (1989) 209–211.
[9] F. Toda, in Y. Ohashi (Ed.), Reactivity in Molecular Crystals, VCH, Weinheim, 1993, p. 177–201.
[10] G.W.H. Höhne, H.K. Cammenga, W. Eysel, E. Gmelin and W. Hemminger, Thermochim. Acta, 160 (1990) 1–12.
[11] H.K. Cammenga, W. Eysel, E. Gmelin, W. Hemminger, G.W.H. Höhne and S.M. Sarge, Thermochim. Acta, 219 (1993) 333–342.
[12] S.M. Sarge, E. Gmelin, G.W.H. Höhne, H.K. Cammenga, W. Hemminger and W. Eysel, Thermochim. Acta, 247 (1994) 129.
[13] R.L. Blaine and C.K. Schoff (Eds.), Purity determination by thermal methods, ASTM STP 838, American Society for Testing and Materials, Philadelphia, 1984.
[14] G.M. Lobanova, Kristallografiya, 13 (1968) 984.
[15] E.B. Fleischer, N. Sung and S. Hawkinson, J. Phys. Chem., 72 (1968) 4311.
[16] M. Epple, S. Ebbinghaus and J. Kopf, to be published.
[17] M. Epple and H.K. Cammenga, Ber. Bunsenges. Phys. Chem., 96 (1992) 1774–1778.
[18] V.I. Saldin, O.V. Brovkina, E.G. Ippolitov and A.P. Popov, Russ. J. Inorg. Chem. (Engl. Trans.), 28 (1983) 273–275.
[19] O. Eisenstein, H.B. Schlegel and M.M. Kayser, J. Org. Chem., 47 (1982) 2886.
[20] W.E. Brown, D. Dollimore and A.K. Galwey, Reactions in the Solid State, Elsevier, Amsterdam, 1980.