Journal of Thermal Analysis and Calorimetry, Vol. 73 (2003) 419–428

POLYMORPHISM OF GLYCINE
Thermodynamic aspects.
Part II. Polymorphic transitions

E. V. Boldyreva [1,2*], *V. A. Drebushchak* [1,3,4], *T. N. Drebushchak* [1,2],
I. E. Paukov [4], *Y. A. Kovalevskaya* [4] *and E. S. Shutova* [1,2]

[1]Novosibirsk State University, Research and Education Research and Education Center 8EC-008,
'Molecular Design and Ecologically Safe Technologies', ul. Pirogova, 2, Novosibirsk 630090, Russia
[2]Institute of Solid State Chemistry, Siberian Branch of Russian Academy of Sciences, ul. Kutateladze,
18, Novosibirsk 630128, Russia
[3]Institute of Mineralogy and Petrography, Siberian Branch of Russian Academy of Sciences,
pr. Koptyuga, 3, Novosibirsk 630090, Russia
[4]Institute of Inorganic Chemistry, Siberian Branch of Russian Academy of Sciences,
pr. Lavrent'eva, 3, Novosibirsk 630090, Russia

Abstract

The contribution summarizes the results of a systematic study of the transformations of the polymorphs of glycine into each another, including the effects of temperature, of the mechanical treatment and of various gases on the transformations.

Keywords: calorimetry, effect of gases, glycine, hydrogen bonds, polymorphic transformations, thermal analysis, X-ray diffraction

Introduction

In [1] the order of relative stability of the three forms of glycine at ambient temperatures ($\beta<\alpha<\gamma$) was found from the variable temperature heat capacity measurements. The next step was to study the possible polymorphic transitions under different experimental conditions: to find if the polymorphs are enantiotropically or monotropically related [2, 3], to find conditions, under which a particular polymorph transforms into another one, to determine the thermodynamic parameters characterizing these phase transformations.

Experimental

Details of the preparation of the samples and of the thermoanalytical, calorimetric and diffraction experiments were described in [1]. For the mechanical treatment, various devices, ranging from a small hand-mortar to a powerful planetary AGO-2 mill and a Fritsch-5 activator were used. For the studies of the effect of gases on the

---

[*] Author for correspondence: E-mail: boldyrev@nsu.ru

1388–6150/2003/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

polymorph transitions, gaseous NH_3 was obtained by heating its concentrated (25%) water solution, purified by $KMnO_4$, activated carbon, and then dried by KOH and $CaCl_2$ [4]. A LOMO microscope with a video-adaptor was used for optical microscopy observations.

Results and discussion

Phase transitions at variable temperature

For the α-polymorph, no phase transitions were observed in the whole temperature range from 5 to 500 K. This agrees with the results of recent variable-temperature structural studies [5, 6] and does not confirm the hypothesis of a phase transition at about 304 K, which was proposed as an explanation of the anomalous electrical behaviour at this temperature [7]. Although the α-form is thermodynamically slightly less stable than the γ-form at low temperatures, its transformation into the γ-form seems to be kinetically hindered.

For the γ-polymorph, an irreversible endothermic phase transition was observed on heating up to 440 K and a reversible endothermic phase transition – on cooling down to 5 K [1]. The high-temperature phase transition gave the α-polymorph, what was proved by X-ray diffraction analysis of the sample after the transition. Earlier Iitaka [8] has observed the γ→α transition at 438±5 K and has estimated the heat of this transformation as less than 2.5 kJ mol^{-1}. Kozhin has also observed the γ→α transition at 438 K [9]. Perlovich *et al.* have observed the γ→α transition in a wide temperature range from 438 to 474 K [10]. The polymorph transition temperatures were shown to be different for various single crystals, and to depend strongly on the size and shape of crystals, on the thermal pre-treatment, on grinding and other mechanical treatment of the crystals. The heat effects of the γ→α transition were also reported to differ from sample to sample (1200±80 J mol^{-1} for T_{tr}=438 K and 1800±80 J mol^{-1} for T_{tr}=453 K) [10].

In our experiments the γ→α transition temperature was also different for different samples. We have carried out a more detailed study of the γ→α transition in glycine, using both powder and single crystal samples, including the samples provided to us by Perlovich. The heat effect of the γ→α transformation studied using a powder sample was found to be described by a curve similar to Gaussian, i.e., to the normal distribution function (Fig. 1). If the measurements were carried out with a small single crystal, the heat effect could be described by a narrow peak (Fig. 1). If large single crystals were studied, the γ→α transformation proceeded in clear ‘jumps’, giving several sharp peaks in the temperature range about 10–15 K (Fig. 1). If the heating of such a large single crystal was stopped at some intermediate time moment, the sample turned out to be partly converted into the α-polymorph. It looked like an opaque pseudomorph preserving the shape of the initial crystal but consisting of disordered blocks of the parent γ- and the product α-forms. Based on our experiments, we can suggest the following possible explanation of the fact, that a long isothermal treatment of the γ-glycine at 432 K has increased the γ→α transition temper-

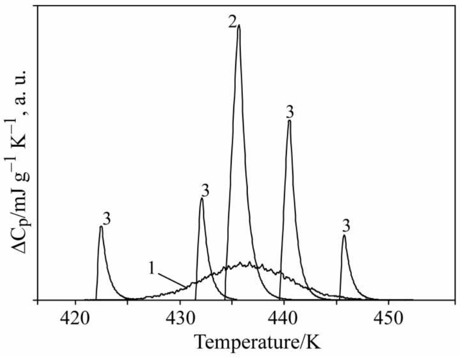

Fig. 1 The heat effect of the γ→α transformation in glycine for different samples: 1 – powder, 2 – an individual small crystal, 3 – a large single crystal

ature from 441 to 455 K [10]: the single crystal of the γ-glycine used in the experiment reported in [10] also transformed heterogeneously, a block after block, and the more reactive blocks have transformed into the α-form earlier, during the pre-treatment. It could be possible to test this explanation, if the heat of the γ→α transformation for this very experiment was reported in [10], but unfortunately it was not. The polymorphic transformations proceeding in a 'jump-wise manner', when different blocks of the same crystal transformed at different temperatures, were previously described for molecular solids by Mnyuch [11, 12].

It is also necessary to keep in mind, that because of the sublimation [1], it is difficult to carry out accurate calorimetric measurements for glycine at the temperature range close to the temperature, at which the γ→α transformation is observed. Any preliminary thermal treatment of the samples will increase the possible error. For example, in [10] it was found, that a long (5 h) preliminary treatment of the γ-glycine at 432 K results in an increase of the γ→α transition temperature from 441 to 455 K. The heat of transition was also reported to change with the transition temperature [10]. Our experiments have shown, that at 432 K the rate of the sublimation of α-glycine is equal to $4\cdot10^{-4}$ % min^{-1}. This means that the mass loss of glycine resulting from an isothermal treatment of glycine at this temperature during 5 h must be about 0.12%. This noticeable surface etching is able to affect the nucleation of the α-glycine during the subsequent γ→α transformation. This can be also a possible reason of the effect of this pre-treatment on the transition temperature, in addition to a partial transformation in the single crystal, that was discussed above.

The low-temperature phase transition in the γ-glycine was never reported previously, and its nature remains unclear (probably related to the piezoelectricity of the γ-form). In relation to a possible phase transition in the γ-glycine at low temperature, it is interesting to note, that a pressure-induced polymorph transition of unknown nature was mentioned in [13, 14], and some reversible spontaneous changes in the powder diffraction patterns of the γ-glycine that might be an indication of a phase transition above 4 GPa were described also in [15].

For the β-polymorph, a reversible endothermic phase transition was observed at about 252 K [1], and an irreversible exothermic transition at about 340 K (Fig. 2) [16]. The latter transition gave the α-polymorph of glycine, as was confirmed by X-ray diffraction of the sample after the transformation. The transition was observed in a wide temperature range, 310–415 K, the total heat release during the transformation being about 200 J mol^{-1}. This value is extremely small and explains why the unstable β-polymorph of glycine can exist at normal conditions for a long time. Comparing our data on heat capacity in the course of the β→α transformation with the data on the enthalpy of solution for the α- and the β-forms, we found that they agree very well with another. Optical microscopy observations have shown the high-temperature phase transition to be heterogeneous; after an induction period an interface propagated rapidly from one face of the crystal to the opposite one; the interface stopped in front of the macroscopic crystal defects and then rounded them. Thus, our study obviously did not confirm the statement published in [10], that 'all the efforts in order to observe a phase transition of the β-glycine in a temperature interval of 25 up to 220°C (for different heating rate and isothermal treatments for about 30 min) were not successful'. We have not only measured the heat of the phase transition at about 340 K, but have also proved that it was a β→α transformation by X-ray diffraction, and have observed this phase transition by optical microscopy. The conclusion that 'the β-form of glycine is monotropically related to other forms' [10] has proved to be erroneous. It is worthy noting that Iitaka also mentioned 'a β→α transformation on heating not higher than 373 K' [8].

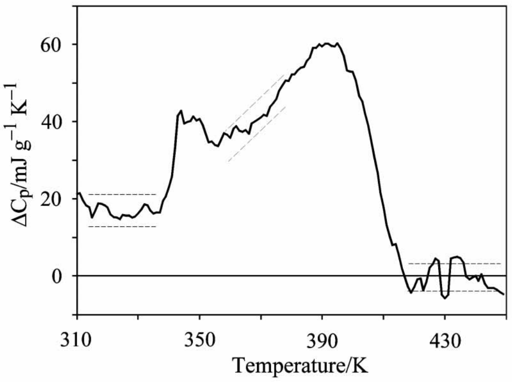

Fig. 2 Difference in the heat capacity between the α-polymorph of glycine (averaged after 7 runs) and the β-polymorph of glycine during its transformation into the α-form. Dashed lines indicate the standard deviations of the $C_p(\alpha)$ measurements [16]

The nature of the low-temperature phase transition in the β-form remains unclear. No indications at a phase transition could be found in an X-ray diffraction study of β-glycine on cooling from ambient temperature down to 105 K [5]. One can suppose the transformation to be a second-order transition involving reorganization of the hydrogen bonds formed by the protons of glycine zwitter-ions, possibly related to the piezoelectric properties of the β-polymorph. Repeated cooling-heating cycles around the phase transition point seem to increase the instability of the β-polymorph and to favour its transformation into the α-form [17].

Phase transitions on storage

Once obtained, neither α-, nor the γ-form were observed to transform into another form on storage at ambient temperature in most publications [9, 18–26]. Iitaka mentioned a spontaneous α→γ transformation at ambient conditions for the deuterated glycine [8]. Only Sakai *et al.* [27] have reported spontaneous transformation of the non-deuterated α-form into the γ-form on storage, and have claimed this process to account for the caking of glycine tablets during storage. At the same time, according to Sakai, the α→γ transformation could be observed only in humid atmosphere (70% relative humidity) and proceeded due to the solubility difference between α- and γ-crystals in the small amount of water at the surface of the α-crystals. The β-polymorph of glycine was reported in several publications to be unstable on storage [8, 9, 28]. According to Iitaka, this form 'has a great tendency to transform into either the α-, or the γ-polymorphs at room temperature, and the transformation is very much accelerated by the presence of water vapor, although the formation of the γ-form was never observed in such a rapid change' [8]. In [10], on the contrary, no transformations of the β-polymorph were observed on storage.

In our experiments both the α- and the γ-forms were preserved at ambient conditions for an indefinitely long time [5, 29, 30]. The crystals of the β-polymorph could be preserved in dry air for several months. This was confirmed not only by optical microscopy observations, but also by several X-ray diffraction data collections during this time period. As the humidity of the air increased, a polymorphic transformation into the α-form was observed. The crystals lost transparency but have preserved their original shape. X-ray diffraction data could be collected from the crystal after the transformation. Reflections became broader after the transformation, than they were in the diffraction pattern from the original crystal, but the structure could be still refined. Orientation matrix after the transformation was determined and the angles between the crystallographic axes of the product α-polymorph with respect to crystallographic axes of the parent β-polymorph were calculated. Molecular layers (normal to *b*-direction) rotated at the angle of about 27° in the course of β→α transformation [29, 30].

Effect of gases on the phase transitions

Gases are known to be able to affect phase transitions, as well as re-crystallization processes in the solids [31–34]. The effect of humidity on the transformations and chemical reactions of glycine was noticed long before the existence of the glycine polymorphs was known and their crystal structures solved [35]. Later on, the effect of humidity on the stability of the glycine polymorphs was repeatedly reported [8, 9, 27, 28]. One could suppose that interactions between vapor molecules and the zwitter-ions at the surface of glycine polymorphs could be strong enough, to influence upon phase transitions between the polymorphs and/or to induce their recrystallization. The enthalpies of transitions are

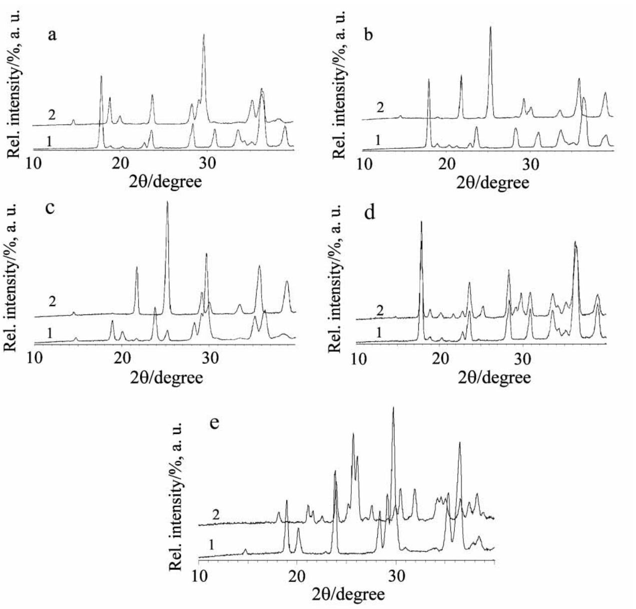

Fig. 3 Powder diffraction patterns measured for the glycine polymorphs before (1) and after (2) the exposure to various gases: a – the β-glycine exposed to H_2O vapor; b – the β-glycine exposed to NH_3, c – the α-glycine with a small admixture of the γ-form exposed to NH_3, d – the β-glycine exposed to NH_4Cl vapor, e – the α-glycine exposed to HCl vapor

rather small (–200 J mol^{-1} for the β→α transition, +1500 J mol^{-1} for the γ→α transition at high temperature, –325 J mol^{-1} as estimated for a hypothetical α→γ transition at ambient temperature). Since a phase transition in the crystalline glycine must be related to a reconstruction of the hydrogen bond network, one could expect, that the ability of a molecule in the gas to form hydrogen bonds with glycine zwitter-ions at the surface of the crystal should be important for the gas to influence upon a reorganization of the crystal structure.

Table 1 Transformations of the α-, β-, and γ-polymorphs of glycine at ambient temperature in the presence of various gases

	EtOH	CH_3COOH	NH_3	H_2O	NH_3+H_2O	NH_4Cl	HCl
α-gly	α-gly	α-gly	α-gly	α-gly	γ-gly (+α-gly)	α-gly	gly·HCl
β-gly	β-gly	β-gly	β-gly	α-gly	γ-gly (+α-gly)	(γ+α+β)-gly	gly·HCl
γ-gly	γ-gly	γ-gly	γ-gly	γ–gly	γ-gly	γ-gly	gly·HCl
(α+γ)-gly	(α+γ)-gly	(α+γ)-gly	(α+γ)-gly	α-gly	γ-gly	(α+γ)-gly	gly·HCl

Following this criterion, we have tested the effect not only of H_2O, but also of NH_3 (dry and wet), CH_3COOH, NH_4Cl, HCl, EtOH on the three polymorphs of glycine [36, 37]. A selected compound was able to contact solid glycine via gaseous phase only. The powder diffraction patterns of glycine were monitored after the contact with a gas was established. The results of the experiments are summarized in Table 1. EtOH, CH_3COOH and dry NH_3 had no effect on all the three forms. Water vapor induced transformation of the β- into the α-form, and did not affect the γ-form (Fig. 3a). In the presence of wet NH_3 the β- and the α-glycine transformed into the γ-polymorph (Figs 3b, c). For the latter transition, the presence of even very small (trace) amounts of the γ-form in the starting α-sample accelerated noticeably the transition. The γ-polymorph (sometimes with the traces of the α-form) was formed as a result of storage of the β-polymorph in the presence of wet gaseous NH_3. The same was true for the storage of the β-polymorph in the presence of NH_4Cl: a mixture of the α- and γ-forms, as well as of the remaining β-form, was observed (Fig. 3d). In the presence of HCl vapor all the three polymorphs of glycine formed crystalline glycine hydrochloride (Fig. 3e). The changes in the two-dimensional powder diffraction patterns allow us to suppose, that the transformations induced in the polymorphs of glycine in the presence of gases are related to the recrystallization of the samples, since the powder patterns become more “spotty” after a sample is kept in the contact with a particular gas (Fig. 4). It is interesting, that dry NH_3 had no effect on the polymorphs of glycine, whereas in the presence of the wet NH_3 polymorphic transformations of the alfa and of the beta-forms into the gamma-form were observed, what is

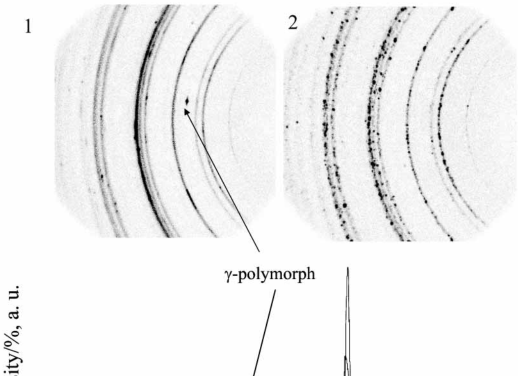

Fig. 4 The two-dimensional (above) and the integrated (below) diffraction patterns of a powder sample of the α-glycine with a small admixture of the γ-form (shown by the arrows). 1 – the initial sample, 2 – the same sample after storage in the presence of water vapor

different from the transitions induced in these polymorphs by pure water vapour (the alfa-polymorph not transforms into any other form, the beta-form transforms into the alfa-form) [37]. In the presence of H_2O and NH_3 gases simultaneously, the samples of glycine became so hydroscopic, that a full dissolution could be observed after a long enough storage. Neither pure water vapour, nor dry NH_3 had such an effect on glycine [37].

Effect of grinding on the phase transitions

Grinding is a stage in preparing the samples for many types of the instrumental studies, and also for processing glycine as a drug. Therefore, it is important to have reliable data on the effect of grinding on the polymorphs of glycine. Contradictory data on the transformations of the glycine polymorphs induced by grinding could be found in the literature. Iitaka has observed that grinding results in the β→α transformation [8]. Perlovich *et al*. have reported the γ→α transformation to be induced by grinding, but they could not observe any β→α transformation [10]. In our experiments we have observed, that grinding of wet (for example, freshly precipitated) β-polymorph resulted in a β→α transformation. At the same time, dry samples of the β-polymorph were stable not only with respect to grinding, but also with respect to a prolonged mechanical treatment in much more powerful mechanical activators, than a mortar (Fritsch-5, AGO-2). The samples of γ-glycine were stable with respect to simple grinding in a mortar, but converted into a mixture of α- and γ-polymorphs after 30 min treatment in the Fritsch-5 activator. Humidity facilitated the γ→α transformation on grinding. The α-polymorph was absolutely stable with respect to grinding [36]. It is remarkable, that both the α- and the γ-polymorphs were shown to be stable with respect to hydrostatic pressure at least up to 4 GPa [15].

Conclusions

The differences in the free energies between the polymorphs of glycine and the heats of transitions between the polymorphs are related to the differences in the weak intermolecular interactions and are therefore rather small. At the same time, the kinetic barriers for the transformations seem to be rather large. This is why, once obtained, the metastable polymorphs can be preserved for indefinitely long time, also at the conditions at which they are not thermodynamically stable. Even the least stable β-polymorph can live long enough in dry atmosphere. Gas molecules (water, NH_3) catalyze the phase transitions between the polymorphs, (β→α, β→γ, α→γ). Initiation of a phase transition plays a very important role. Therefore the transitions are so sensitive to the presence of even traces of another polymorph, as well as to the impurities or structural defects in the glycine crystal. The mechanisms of the transitions, which must involve some cooperative reorganization of the whole hydrogen bonded network in the crystal, require further detailed studies, and so do the mechanisms of the effect of gases and of the mechanical treatment on the polymorphs. Model computer simulations [38, 39] can be helpful for this purpose. In turn, the experimental thermodynamic and structural variable-temperature and variable-pressure data can be used to work out better potentials describing the interatomic interactions in the glycine polymorphs and to test the predictive power of the simulations [5, 15].

* * *

The study was supported by RFBR (grant 02-03-33358), by BRHE (a joint grant REC-008 of CRDF and Russian Ministry of Education), by the Russian Ministry of Education (grant Ч0069 'Integration', grant 1-67-01), and by the programs of the Presidium of Russian Academy of Sciences. The authors thank Dr. G. Perlovich for providing them a sample of γ-glycine and A. Achkasov for the assistance with the experiments with gaseous NH_3.

References

1 E. V. Boldyreva, V. A. Drebushchak, T. N. Drebushchak, I. E. Paukov, Yu. A. Kovalevskaya and E. S. Shutova, J. Therm. Anal. Cal., 73 (2003) 409.
2 W. C. McCrone, in: Physics and Chemistry of the Organic Solid State, Vol. 2, D. Fox, M. M. Labes, A. Weissberger (Eds), Interscience, New York 1965, p. 726.
3 J. Bernstein, Polymorphism in Molecular Crystals. IUCr Monographs on Crystallography 14, Oxford Science Publications, Clarendon Press Oxford, 2002, p. 410.
4 G. Brauer (Ed.) Handbuch der Präparativen Anorganischen Chemie (1954) Redinand Enke Verlag, Stuttgart, p. 896.
5 E. V. Boldyreva, T. N. Drebushchak and E. S. Shutova, Z. Kristallogr., 218 (2003), issue 5, in press.
6 P. Langan, S. A. Mason, D. Myles and B. P. Schoenborn, Acta Cryst., 58B (2002) 728.
7 T. C. Chilcott, B. P. Schoenborn, D. W. Cooke and H. G. L. Coster, Phil. Mag., B79 (1999) 1695.
8 Y. Iitaka, Acta Cryst., 14 (1961) 1.
9 V. M. Kozhin, Kristallografiya (Sov. Crystallography), 23 (1978) 1211.
10 G. L. Perlovich, L. K. Hansen and A. Bauer-Brandl, J. Therm. Anal. Cal., 66 (2001) 699.
11 A. I. Kitaigorodskiy, Yu. V. Mnyukh and Yu. G. Asadov, J. Phys. Chem. Solids, 26 (1965) 463.
12 Yu. V. Mnyukh, Mol. Cryst. Liq. Cryst., 52 (1979) 163.
13 R. J. Nelmes, J. S. Loveday, M. Guthrie and D. J. Francis, ISIS Experimental Report, Rutherford Appleton Laboratory, RB N. 10795 (2000).
14 A. Dawson, S. Parsons, D. Allan, J. Loveday and M. Guthrie, Glycin. A new high pressure phase [http://www.isis.rl.ac.uk/BCA2001/Abstract%20files/bca1...].
15 E. V. Boldyreva, H. Ahsbahs and H.-P. Weber, Z. Kristallogr., 218 (2003) 231.
16 V. A. Drebushchak, E. V. Boldyreva, T. N. Drebushchak and E. S. Shutova, J. Cryst. Growth, 241 (2002) 266.
17 I. E. Paukov, V. A. Drebushchak, T. N. Drebushchak, E. V. Boldyreva, Yu. A. Kovalevskaya, E. S. Shutova and A. F. Achkasov, unpublished data.
18 J. D. Bernal, Z. Krist., 78 (1931) 363.
19 J. Hengstenberg and F. V. Lenel, Z. Krist., 77 (1931) 424.
20 A. I. Kitaigorodskii, Zhurn. Fiz. Khim. (Russ. J. Phys. Chem.), 8 (1936) 756.
21 G. Albrecht and R. B. Corey, J. Amer. Chem. Soc., 61 (1939) 1087.
22 R. E. Marsh, Acta Cryst., 11 (1958) 225.
23 P.-G. Joensson and A. Kvick, Acta Cryst., B28 (1972) 1827.

24 J. Almlof and A. Kvick, J. Chem. Phys., 59 (1973) 3901.
25 L. F. Power, K. E. Turner and F. H. Moore, Acta Cryst., B32 (1976) 11.
26 I. Weissbuch, R. Popovitz-Biro, M. Lahav and L. Leiserowitz, Acta Cryst., B51 (1995) 115.
27 H. Sakai, H. Hosogai, T. Kawakita, K. Onuma and K. Tsukamoto, J. Cryst. Growth, 116 (1992) 421.
28 Y. Iitaka, Acta Cryst., 13 (1960) 35.
29 T. N. Drebushchak, E. V. Boldyreva, Yu. V. Seretkin and E. S. Shutova, Russ. J. Struct. Chem., 43 (2002) 892.
30 T. N. Drebushchak, E. V. Boldyreva and E. S. Shutova, Acta Cryst., E58 (2002) 634.
31 B. F. Ormont, Russ. J. Phys. Chem., 21 (1947) 569.
32 M. A. Khachvankyan and B. F. Ormont, Russ. J. Phys. Chem., 21 (1947) 575.
33 P. T. Cardew and R. J. Davey, Proc. R. Soc. Lond., A398 (1985) 415.
34 S. P. Duddu, T. D. Sokoloski, N. G. Das, M. E. Morris, K. H. Patel and C. S. Randall, Pharm. Res., 11 (1994) 153.
35 C. A. Brautlecht and N. F. Eberman, J. Amer. Chem. Soc., 45 (1923) 1934.
36 E. S. Shutova, Graduation paper, Novosibirsk State University (2002).
37 E. V. Boldyreva, E. S. Shutova, T. N. Drebushchak and A. F. Achkasov, unpublished results.
38 A. Peeters, C. Van Alsenoy, A. T. H. Lenstra and H. J. Geisa, J. Chem. Phys., 103 (1995) 6608.
39 Z. Berkovitch-Yellin, J. Amer. Chem. Soc., 107 (1985) 8239.