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Radiation-induced radicals in different polymorphic modifications of D-mannitol: Structure, conformations and dosimetric implications

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HIGHLIGHTS

- Radicals in irradiated D-mannitol were characterized by EPR.
- Effect of molecular packing on radical conformations was studied.
- Applications of D-mannitol as a prospective EPR dosimeter are discussed.

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ABSTRACT

The structure and conformation of radicals produced by X-ray irradiation of three polymorphic forms of D-mannitol were investigated using EPR spectroscopy. In all the cases, primary species were identified as radicals resulting from hydrogen abstraction from position 3 or 4 of the mannitol molecule. It was found that molecular packing in crystals of different polymorphic modifications had noticeable effect on the conformation of radicals observed after irradiation at room temperature and the dehydration of the primary radicals occurring at 400 K. The radicals trapped in stable modifications (β- and δ-forms) were found to be very stable at room temperature. Relatively high radical yields and remarkable stability of radicals suggest that D-mannitol can be used as an EPR dosimeter or irradiation marker.

1. Introduction

D-mannitol is an acyclic sugar alcohol found in seaweed, grass, fruits, and fungi. It is used as a medicine for the treatment of brain edema and as an excipient for some drugs, which are subjected to the radiation sterilization. Irradiation of mannitol produced free radicals, which are stable enough under ambient conditions. In particular, it was shown that irradiation of some medical compositions containing mannitol to typical sterilization doses (10–25 kGy) led to accumulation of stable radicals readily detectable by EPR spectroscopy (Maksimenko et al., 2008). These radicals may serve as "markers" of irradiation of the corresponding specimens. Furthermore, there is a certain potential for using mannitol as an EPR dosimeter for pharmaceutical and other applications. It is worth noting that a recent review in the field of EPR dosimetry (Yordanov et al., 2012) indicates several examples of the dosimetrically targeted studies on crystal carbohydrates (e.g., glucose Yordanov and Georgieva, 2004); meanwhile, we are unaware of any attempts to apply mannitol for these purposes. Earlier investigations of the radicals produced in irradiated mannitol revealed the formation of radicals produced by hydrogen abstraction atom from position 3 or 4 of the mannitol molecular chain (Fig. 1) (Makarov and Ershov, 1970; Nikitin et al., 1972).

It was reported that the radicals produced from D-mannitol underwent dehydration upon heating above 373 K (Kochetkov et al., 1979) presumably resulting in the formation of the RO· type radicals (Nikitin et al., 1972), however, the chemical transformations and stability of these species were not studied in detail. A remarkable feature of mannitol (unusual among carbohydrates) is an existence of several polymorphic crystalline forms (α, β and δ). In fact, the polymorphism of D-mannitol was investigated through more than one hundred years, but the identification of the polymorphic forms was still under discussion until recently (Burger et al., 2000). The beta modification is known to be the most thermodynamically stable; however, the delta form shows a superordinary kinetic stability, so it can exist for years without any observable transformation (Burger et al., 2000). On the other hand, the alpha modification is metastable and converts to the beta form

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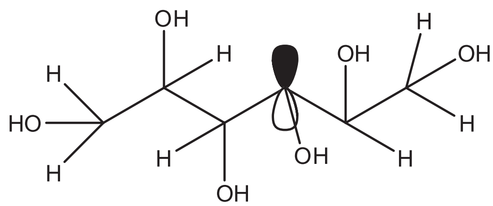

Fig. 1. Structure of radicals in D-mannitol irradiated at 77 K or 298 K.

in the timescale of hours, especially in moisture conditions Yoshinari et al., 2002. It is clear that polymorphism may affect strongly the geometrical configuration of the radiation-induced radicals in D-mannitol and their stability and chemical transformations, which is of considerable interest from both fundamental and practical points of view (particularly, in the application of this substance for the EPR dosimetry). However, to our knowledge these aspects were not considered in the previous studies. The aim of this work was to investigate the structure and conformation of radicals produced by X-ray irradiation at 298 and 77 K in different polymorphic modifications of D-mannitol and to access their stability and their thermal transformations up to 400 K. Also, we discuss the implication of the results for potential practical applications using D-mannitol as a radiation sensitive material.

2. Material and methods

The polymorphic modifications of D-mannitol were characterized by Raman spectroscopy as described elsewhere (Xie et al., 2008). The commercial sample of D-mannitol obtained from Reachim (pure) was identified as δ form. The α form was obtained by fast nucleation of saturated at 353 K aqueous solution of D-mannitol with acetone and the β form was prepared by slow crystallization of saturated at 298 K aqueous solution of D-mannitol in the refrigerator (Burger et al., 2000; Campbell Roberts et al., 2002). The mannitol powders were placed into SK-4B glass tubes, which gave no background EPR signal at $g \approx 2$ after irradiation. The samples were irradiated in open air at 298 K or in vacuum at 77 K (in the latter case, the samples were evacuated to a residual pressure of 0.1 Pa at room temperature and then immersed in liquid nitrogen in a Dewar vessel). Irradiation was carried out with a 5-BKhW-6(W) X-ray tube with tungsten anode (applied voltage 32 kV, anode current 70 mA). The absorbed dose was determined using the ferrosulfate dosimetric solution (Fricke dosimeter) irradiated in similar tubes in the same geometry and recalculated for mannitol taking into account the mass absorption coefficients at the effective energy of X-rays of ca. 20 keV:

$$D_{man} = D_{Fe} \cdot \frac{(\mu/\rho)_{man}}{(\mu/\rho)_{Fe}} \quad (1)$$

Here D_{man} and D_{Fe} are the absorbed dose of X-ray irradiation for mannitol and dosimetric solution, respectively, $(\mu/\rho)_{man} = 0.35$ and $(\mu/\rho)_{Fe} = 0.55$ are the mass absorption coefficients for mannitol and dosimetric solution (the latter one being almost equal to that of water), respectively, at $E = 20$ keV (Hubbell and Seltzer, 1996). In order to estimate the dose for irradiation at 77 K, the tube with dosimetric solution was placed in the same Dewar vessel filled with ethanol, which has the mass attenuation coefficient for X-rays close to that of liquid nitrogen. The dose rate was found to be 5.0 Gy/s for irradiation at 298 K and 1.9 Gy/s for irradiation at 77 K and the total absorbed dose was 4.8–5.2 kGy (irradiation at 298 K) and 2.1–2.5 kGy (irradiation at 77 K).

The EPR spectra were recorded with an X-band (9.4 GHz) spectrometer (SPIN, Russia) with a 100-kHz high-frequency modulation. The microwave power level was typically 0.5 mW in most experiments and varied between 0.15 mW and 3 mW for the microwave saturation studies. EPR spectra were simulated in isotropic approximation using a WinSim program (Duling, 1994).

The relative intensity of EPR signal was calibrated using the synthetic ruby (Al_2O_3 doped Cr^{3+} ions) as an internal reference sample, which is located inside the resonator cavity. The signal from ruby does not overlap with the signal of organic radicals from irradiated mannitol due to large difference of *g*-values. For each sample, the integrated intensity of the signals from D-mannitol was normalized to the amplitude of signal from ruby recorded under the same conditions. The total number and concentration of paramagnetic species in irradiated sample were estimated using known amount of paramagnetic salt $CuCl_2 \cdot 2H_2O$ as an absolute standard with spin 1/2.

In the case of annealing studies, the irradiated samples were annealed at 400 K for 10 min and then cooled down to room temperature. After cooling to room temperature EPR spectra of radicals were recorded.

3. Experimental results and discussion

3.1. Irradiation at 77 K

EPR spectra of all polymorphic forms irradiated and measured at 77 K are shown in Fig. 2. Basically, these patterns are qualitatively similar and they represent a broad, poorly resolved doublet with a hyperfine splitting of approximately 2.5 mT, close to that reported previously for D-mannitol of unknown polymorphic modification (Makarov and Ershov, 1970). Detailed conformational analysis of these spectra is hardly possible because of severe line broadening. Meanwhile, the spectral pattern implies that only one of two beta-protons strongly interacts with unpaired electron (more detailed discussion of possible conformations will be presented below). It is known that the conformation of molecules in non-irradiated D-mannitol for different modifications are similar (Fronczek et al., 2003). Thus, it is logical to assume that the radicals obtained after irradiation at 77 K have nearly the same conformation because of hindered structure relaxation at low temperature, which results in roughly similar EPR spectra.

3.2. Irradiation at 298 K

EPR spectra of radicals produced from different forms of mannitol irradiated at 298 K are similar to signals obtained for the samples heated to room temperature after irradiation at 77 K. In

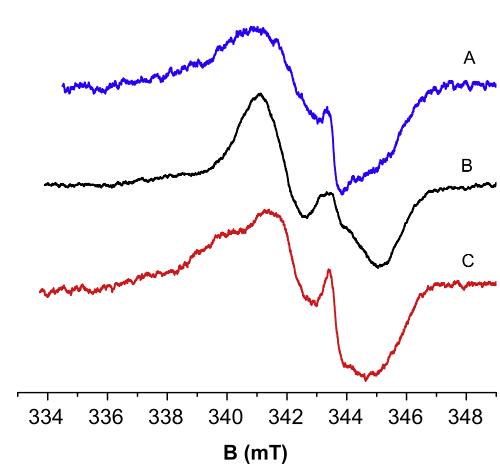

Fig. 2. EPR spectra of polymorphic forms of D-mannitol irradiated at 77 K. A – α-D-mannitol; B – β-D-mannitol; C – δ-D-mannitol.